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Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
Room 3118
79 Alexander Drive, Bldg. 12233
Research Triangle Park, NC 27709

June 24, 2004

JUN 25 2004

RE: 12th Report of Carcinogens (RoC) Nomination – Public Comment
OCCUPATIONAL EXPOSURE TO TALC

Dear Dr. Jameson:

R. T. Vanderbilt Company, Inc. ("Vanderbilt") and its wholly owned subsidiary, Gouverneur Talc Company, Inc. are engaged in the mining, milling and marketing of industrial talc that is used primarily in the paint and ceramic industries. Vanderbilt appreciates the opportunity to comment on the captioned National Toxicology Program (NTP) nomination.

Vanderbilt was an active participant in the 10th RoC review of talc, testified at the public hearing before the NTP's Board of Scientific Counselors RoC Subcommittee and submitted extensive written comments dated June 2, 2000 and July 8, 2002. Vanderbilt assumes that all pertinent submissions for the 10th RoC talc nomination will be reviewed for the 12th RoC nomination. For convenience, our 2000 and 2002 comments are resubmitted with this correspondence. However, all referenced studies in these submissions are not again included. If there is a need for copies of these studies please contact the undersigned.

The NTP deferred the 10th RoC "asbestiform and non-asbestiform talc" nominations because, among other things, it found excessive ambiguity in the scientific literature regarding the meaning of these terms. Many who submitted comments on the 10th RoC, recognized these important mineral nomenclature issues.

Vanderbilt notes that the talc nomination for the 12th RoC has been changed to "cosmetic talc" and "occupational exposure to talc". It is assumed that these nominations refer to the mineral talc per se, and not to asbestos. Vanderbilt further assumes that the nomination does not include mixed mineral dust exposures in which talc is a minor or insignificant component. In effect, we hope oversights made during the 10th RoC review of talc are not repeated in the 12th RoC review of talc.

Clear exposure characterization is of particular importance when addressing occupational exposures in the mining industry. Mineral dust exposures can vary widely in the production of a single mineral end product. Within a single mine or a single mining operation, mineral dust exposures can vary in composition within a yard of each other. Unlike chemical processing, mining rarely if ever presents a truly homogenous workplace exposure. Mixed dust exposures are also common in industries that use talc.

The basis for the "occupational exposure to talc" nomination is listed as "human epidemiological studies reporting an increase risk of cancer among workers exposed to talc." Historically, whenever this reference is made, it is often followed by a discussion of mortality studies involving New York State tremolitic talc miners and millers. Indeed, Vanderbilt talc workers are among the most studied group of miners in the world. While every animal or cell study that has tested Vanderbilt's talc for carcinogenicity is negative (**refs. 1-3**), every mortality study of these talc workers does show a moderate and persistent excess lung cancer rate (**refs. 4 –10).**

As explained during the 10th RoC review of talc, the use of Vanderbilt talc worker studies to establish evidence of talc carcinogenicity is problematic on two fronts. ***Firstly***, the mineral talc itself represents no more than 30 to 40% of the mineral dust exposure (typically in the 30% range) (**refs. 11-14).** This is not a pure (or even mostly pure) talc exposure and it is therefore not appropriate for use in assessing a carcinogenic risk to talc per se. ***Secondly***, the etiology of the excess lung cancer noted among Vanderbilt talc workers has been interpreted in conflicting ways. While the earliest studies suggest that the excess lung cancer among New York State talc miners and millers was caused by dust exposure to the ore (**ref. 4),** the most recent and more exhaustive studies argue against this association ***regardless of the dust's mineral composition*** (**refs. 9, 10**). Dr. Elizabeth Delzell, a principle author on the most recent mortality study of Vanderbilt talc workers, informed the NTP of this finding in November of 2000 (**ref. 15**). Dr. John Gamble and Dr. Graham Gibbs also provided comments to the NTP on this subject in 2000 (**refs. 16, 17).**

As explained in Vanderbilt's previous submissions, the principal reason for suggesting a dust/cancer association in earlier studies of Vanderbilt talc workers was the mistaken belief that Vanderbilt talc contained asbestos. In actual fact, Vanderbilt's talc does not contain asbestos (**ref. 11-14, 18, 19).** Vanderbilt does not know the mineral composition of other industrial grade talc mined earlier and in other regional mines. Since 1974, Vanderbilt has operated the only tremolitic talc mine in New York State. The association of asbestos in talc has been a persistent but largely inappropriate concern for decades. Since asbestos is already listed by the NTP as a known human carcinogen, we hope the matter of asbestos (real or imagined) will not be a part of the 12th RoC review of talc.

Appended is a list of studies we believe are the most applicable to NTP's current "occupational exposure to talc" nomination. These pulmonary cancer studies involve human and animal studies that appear to involve pure or predominant talc exposures. We believe a review of these studies lends no support for a causal link between exposure to the mineral talc and cancers of the pulmonary system.

Human and animal studies that involve significantly mixed mineral dust exposures with talc but do not support a pulmonary cancer risk due to this exposure, provide no support for talc as an occupational carcinogen as well. Vanderbilt talc studies would be among such studies. Mixed exposures ***that do*** appear to be causally linked to pulmonary cancers cannot be used to support or reject talc as an occupational carcinogen. A listing of these mixed dust studies is appended as well.

Vanderbilt intends to fully participate in this NTP nomination, and looks forward to providing additional comment when appropriate.

Sincerely yours,

R. T. VANDERBILT COMPANY, INC.

John W. Kelse, Corporate Industrial Hygienist
Manager, Corporate Risk Management Dept.

REFERENCES: (Full Text Appended)

1. Smith, WE. et al: *Biologic Tests of Tremolite in Hamsters.* In "Dusts and Diseases" R. Lemen and J. Dement, editors. Pathotox Pub. Park Forest S. IL (1979) pp 335-339.

2. Stanton, MF. et al: *Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestos and Other Fibrous Minerals.* JNCL (1981) Vol. 67. No. 5 pp 965-975.

3. Wylie, AG. et al: *Mineralogical Features Associated with Cytotoxic and Proliferative Effects of Fibrous Talc and Asbestos on Rodent Tracheal Epithelial and Pleural Mesothelial Cells.* Tox & App Pharm. (1997) 147 Article No. TO978276

4. National Institute for Occupational Safety and Health: *Occupational Exposure to Talc Containing Asbestos.* Brown, DP. et al (1980) NIOSH Pub. No. 80-115.

5. Stille, WT. et al: *The Mortality Experience of Upstate New York Talc Workers.* J Occ. Med. (1982) Vol. 24 No. 6. pp 480-484

6. Lamm, SH. et al: *Analysis of Excess Lung Cancer Risk in Short-Term Employees.* Am J. of Epi. (1988) Vol. 127 No. 6 pp. 1202-1209.

7. Lamm, SH. et al: *Similarities in Lung Cancer and Respiratory Disease Mortality of Vermont and New York State Talc Workers.* Proceedings of the 11th International Pneumoconiosis Conference (1988) Epidemiology/Fibers, pp. 1576-1581.

8. National Institute for Occupational Safety and Health: Health Hazards Evaluation Report. Brown, DP. et al. (1990) HETA 90-390-2065 MHETA 86-012-2065.

9. Gamble, J.: *A Nested Case Control Study of Lung Cancer among New York Talc Workers.* Int. Arch. Occ. Env. H. (1993) Vol. 64 pp. 449-456

10. Yasushi, H. et al: *Mortality among Workers at a Talc Mining and Milling Facility.* Ann. Occup. Hyg. (2002) Vol. 46. No. 7. pp. 575-585.

11. Kelse, JW. et al: *The Regulatory and Mineralogical Definitions of Asbestos and their Impact on Amphibole Dust Analysis.* Am Ind Hyg Assoc J. (1993) 50 613-622

12. Letter to Greg Piacitelli (NIOSH) from Dan Crane (OSHA Lab.) dated 11/26/86.

13. Wyle, AG. et al: *The Importance of Width in Asbestos Fiber Carcinogenicity and its Implications for Public Policy.* Am Ind Hyg Assoc J. (1993) 54 239-252.

14. R. T. Vanderbilt Company, Inc. Material Safety Data Sheet for *NYTAL® 400*

15. Submission to the NTP from Elizabeth Delzell, SD and Kent Oestenstad, PhD concerning the 10th RoC Nomination "Talc Containing Asbestiform Fibers" Nov. 29, 2000.

16. Submission to the NTP from John F. Gamble, PhD concerning the 10th RoC Nomination "Talc Containing Asbestiform Fibers" Dec. 2000.

17. Submission to the NTP from Graham W. Gibbs, PhD concerning the 10th RoC Nomination "Talc Containing Asbestiform Fibers:" Nov. 28, 2000.

18. Submission to the NTP from GL Nord, PhD, CW Axten PhD CIH, RP Nolan, PhD concerning the 10th RoC Nomination "Talc Containing Asbestiform Fibers" *Mineralogy and Experimental Animal Studies of Tremolitic Talc* Dec.1, 2000.

19. Letter to Bruce Mandel from Ann G. Wylie, PhD concerning the mineral composition of Vanderbilt talc. March 17, 1995.

Pulmonary Cancer Studies (human and animal) that appear to involve exclusive or predominant exposure to talc:

Coggiola, M. et al: ***An Update of Mortality Study of Talc Miners and Millers in Italy.*** **Am. J. of Ind. Med: (2003) 44:63-69.**

Wild, P. et al: ***A Cohort Mortality and Nested Case-Control Study of French and Austrian Talc Workers.*** **Occup. Environ Med (2002) 59:98-105.**

National Toxicology Program: ***Toxicology and Carcinogenesis Studies of Talc (CAS 14807-96-6 Non-Asbestiform) in F344/N Rats and B6C3Fi Mice.*** **TR-421, Research Triangle Park, NC (1993).**

Wergeland, E. et al: ***Mortality and Morbidity in Talc-exposed Workers.*** **Am J Ind Med (1990) 17:505-513.**

Leophonte, P.: ***Mortality of Talc Workers in France – Retrospective Epidemiological Study. Rev Fr Mal Resp. (1983) 11:489-490.***

Stanton, MF, et al: ***Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestos and Other Fibrous Minerals.*** **Talc samples 1-5 (only). JNCL (1981) Vol. 67 No. 5:965-975**

Rubino, GF. et al: ***Mortality and Morbidity Among Talc Miners and Millers in Italy.*** **In Lemon R. Dement JM, Editors. Dusts and Disease (1979) Ill. USA: Pathotox 357-363.**

Selevan, SG. et al: ***Mortality Patterns Among Miners and Millers of Non-asbestiform Talc.*** **Preliminary Report in Lemon R., Dement JM, Editors. Dusts and Disease (1979) Ill. USA: Pathotox 378-388.**

Chappell, AG. et al: ***A Survey of the Long-term Effects of Talc and Kaolin Pleurodesis.*** **Brit J of Dis of the Chest (1979) 73, 285. Chappell, AG. et al:** ***A Survey of the Long-term Effects of Talc and Kaolin Pleurodesis.*** **Brit J of Dis of the Chest (1979) 73, 285.**

Wagner, AP. et al: ***Animal Experiments with Talc.*** **In In haled Particles W. H. Walton and B. McGovern, Editors (1977) Pergamon Press, Oxford Vol. IV Part 2:647-654.**

Wehner, AP. et al: ***Inhalation of Talc Baby Powder in Hamsters.*** **Food Cosmet. Toxicol. (1977) Vol. 15:121-129.**

Pulmonary cancer studies (human and animal) that involve mixed dust exposures with talc as a miner, or possibly miner component:

R. T. Vanderbilt Company, Inc. New York State Tremolitic Talc Studies in Animals and Cells - Submission references: 1-3.

R. T. Vanderbilt Company, Inc. New York State Tremolitic Talc Studies in Miners and Millers – Submission references: 4-10.

Morgan, RW. et al: ***A General Mortality Study of Production Workers in the Paint and Coatings Manufacturing Industry.*** **J Occ Med. (1981) 23:13-21.**

Thomas, TL. et al: ***Mortality from Lung Cancer and Respiratory Disease Among Pottery Workers Exposed to Silica and Talc.*** **Amer J Epi (1987) 125:35-43.**

Kleinfeld, MD. et al: ***Mortality Experiences Among Talc Workers: A Follow-up Study.*** **J occ med. (1974) 16:345-349.**

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June 2, 2000

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

RE: 10th ROC NOMINATIONS – PUBLIC COMMENT
Talc (containing asbestiform fibers)

Dear Dr. Jameson:

R. T. Vanderbilt Company, Inc. ("Vanderbilt") and its wholly-owned subsidiary, Gouverneur Talc Company, are engaged in the mining, milling and marketing of industrial talc that is used primarily in the paint and ceramic industries. Vanderbilt appreciates the opportunity to comment on the captioned NTP nomination. We believe that the available evidence does not support the need for a separate entry for talc containing asbestos or asbestiform fibers. Such an entry would suggest to the public that this is a real and far reaching exposure potential, when in reality it is extremely rare (if it occurs at all). While talc containing asbestos or asbestiform fibers may be perceived as a substantial cancer threat, in reality, such a threat is not reasonably supported. Further, there is no need to consider the carcinogenicity of asbestos, since the latter is already listed. Vanderbilt's comments are divided into two main areas: Nomenclature and Justification. We have also appended several reference documents which are organized under general topic tabs as well.

NOMENCLATURE

The entry "talc containing asbestiform fibers" is misleading. If the entry means the mineral talc contaminated with "asbestos," it would be more clearly expressed as "talc containing asbestos". That change would also be consistent with the way most government agencies and mineral scientists describe this mineral category. For example, the Occupational Safety and Health Administration (OSHA) uses the phrase "talc containing asbestos" in its current Permissible Exposure Limits Tables (OSHA ref. 1, Tab 1). The American Conference of Governmental Industrial Hygienists (ACGIH) expresses the exposure in the same way in its Threshold Limits Values for Chemical Substances and Physical Agents (ACGIH ref. 2, Tab 1). The Environmental Protection Agency (EPA) also addresses the exposure as "asbestos" (ref. 3, tab 1).

The NTP currently lists asbestos as a known human carcinogen. Accordingly, any material containing asbestos would reasonably be assumed to pose a carcinogenic risk, depending upon the amount of asbestos involved, the duration of exposure, the type of asbestos involved, the route of entry, etc. The origin of this entry is understood to be Supplement 7 (1987) to the International Agency for Research on Cancer (IARC) which characterizes the exposure as "talc containing asbestiform fibers". However, this IARC reference is neither up to date nor accurate. The studies noted in Supplement 7 have been superseded by a more advanced understanding of mineral nomenclature and biological issues concerning talc and asbestos.

The word "asbestos" is a commercial term applied to six specific minerals, but only when they exhibit an "asbestiform" crystal growth structure or "habit". The asbestiform crystal growth pattern is extremely rare in nature, and the six minerals are far more abundant in their nonasbestiform habit. When these six minerals do not exhibit asbestiform crystal growth they are not classed as asbestos. In their far more common nonasbestiform habit some of these minerals are called by other names even though chemically and structurally (internal structure) they are the same mineral. (See references 4 to 9 tab 2 and references 10 and 12 Tab 3 for a more complete discussion.) The amphibole minerals tremolite, anthophyllite and actinolite are called by the same name, regardless of their crystal growth habit.

In addition to the six asbestos minerals, many minerals (including the mineral talc itself) can be found in nature in an asbestiform "habit" (Steel et al, ref 5, Tab 2). Such occurrences, however, are rare. When growing in this habit, these minerals share the same basic external crystal growth structure as the six asbestos minerals, but differ in other respects (physio-chemical properties, harshness, durability, etc.). It is therefore misleading to use the term "asbestiform" as a synonym for asbestos. "Asbestiform" refers only to a crystal growth habit. Mineral scientists from academia, government and industry have taken great pains to describe these distinctions (see references 4 to 9, Tab 2 and 10 and 11, Tab 3), but confusion still exists.

As pointed out by Campbell et al (U.S. Dept. of Interior, ref. 4, Tab 2), "Precise definitions acceptable to mineral analysts, regulatory personnel, and medical scientists are essential because of the present lack of conformity in terminology concerned with measuring and controlling asbestiform particulates and their related health effects". The meaning of terms like "fiber", "asbestos" and "asbestiform" are unfortunately unclear to many health investigators. Such ambiguity can lead to misleading exposure characterization in health studies involving elongated particles.

One series of studies, prominently referenced in the NTP cited IARC supporting monograph, exemplifies error. These references involve early mortality studies conducted by Kleinfeld, et al (ref. 38, tab 5) and NIOSH (Brown, et al ref. 36, tab 5) on upstate New York tremolitic talc miners and millers. The NIOSH study exclusively involves Vanderbilt talc miners and millers.

In these studies NIOSH incorrectly characterized nonasbestiform amphibole cleavage fragments as asbestos, as they had previously done in another study involving amphibole

minerals (Homestake Gold mining study – see ref. 24, tab 5 pp. 38-39). Much of the concern involving asbestos in talc originated from this erroneous characterization by NIOSH. Over the years, however, this complex mineral mix has been studied by many highly regarded analysts who repeatedly confirmed the absence of asbestos in this talc (see references 10 to 14, tab 3 and reference 17, tab 4).

The nonasbestiform amphibole controversy associated with these talc worker studies spanned several decades and was ultimately the center of a protracted OSHA rulemaking process. This rulemaking culminated in an OSHA final rule in 1992 which stated that substantial evidence is lacking to conclude that nonasbestiform tremolite, anthophyllite and actinolite present the same type or magnitude of health risks as asbestos (OSHA ref.. 8 tab 2). The complete OSHA record, which includes extensive mineral nomenclature discussion and health study reviews pertinent to this NTP review can be obtained under Docket H-033-d of the Occupational Safety and Health Administration; 200 Constitution Avenue N.W.; Room N2625; Washington, DC (OSHA ref.. 8, tab 2).

In its rulemaking, OSHA recognized the key mineral distinctions discussed above and specifically acknowledged that the mineral composition of Vanderbilt talc was in fact correctly stated on the company's Material Safety Data Sheet and that this talc did not contain asbestos (MSDS ref. 15, tab 3). Prior to the final OSHA rulemaking, a more accurate understanding of the actual composition of this talc was recognized by OSHA's own laboratory (Crane letter ref. 11, tab 3). This is the same talc incorrectly characterized in the IARC monograph as "asbestos-containing". We urge that the NTP not perpetuate this error.

If any particular nonasbestos mineral caused the same health effects as asbestos, it would certainly be important to regulate and control that mineral exposure just as asbestos is controlled. However, we should not confuse cause and effect associations and "mechanism" studies designed to predict risk by obscuring (rather than clarifying) the nature of the exposure. For this reason throughout the years, Vanderbilt and others have repeatedly appealed to health researchers to use proper mineral nomenclature when addressing health effects. As discussed by Dr. Campbell (supra), it is critically important to call things what they are.

If the intent of the "talc containing asbestiform fibers" entry is to characterize and evaluate the carcinogenic risk of talc containing asbestos, the entry should specifically say "talc containing asbestos". Alternatively, the entry might be deleted altogether since asbestos is already listed as a known human carcinogen. The IARC references underlying the nomination suggest that actual "asbestos" exposure is being discussed (valid characterization or not).*

* If the intent is to address any mineral in the asbestiform habit, then risk information for asbestiform minerals other than asbestos would need to be addressed and be reasonably shown to have a carcinogenic effect (such as that shown for asbestos).

JUSTIFICATION

Should the NTP continue with the entry "talc containing asbestiform fibers" as a known human carcinogen, justification for that entry needs to be addressed. Presently, there is scant support for such an entry. A review of the 1987 IARC Supplement monograph in which this mineral combination was characterized as a known human carcinogen reflects the following supporting references and arguments.

a. Asbestos was found in assorted, off-the-shelf cosmetic talcs in the 1970's (Rohl, et al), posing a risk to general consumers and supporting the perception that asbestos is a common contaminant in talc.

b. Asbestos was reported by NIOSH in New York State industrial grade tremolitic talc, posing a risk to miners and millers as well as industrial users of this talc (ceramics, paint, etc.). See Brown, et al, ref. 36, tab 5.

c. The asbestos NIOSH reported in New York talc (tremolite and anthophyllite specifically) was said to be the etiologic agent in the elevated lung cancer observed in these talc miners (Brown, et al ref. 36, tab 5). Earlier studies of New York talc miners from the same region showed a similar lung cancer excess (Kleinfeld, ref. 38, tab 5).

d. Four case reports of mesothelioma were said to be linked to upstate New York talc mining (Vianna, 1981).

Each of these references is addressed below.

A. Asbestos was found in some cosmetic talcs and may therefore be a common contaminant in talc.

Reports of trace asbestos found in some off-the-shelf samples of cosmetic talc appeared in the 1970's through the work of Mt. Sinai researchers (Rohl, et al). At that time the principal researcher (Rohl) also found asbestos in New York State tremolitic talc (Vanderbilt talc) in support of the NIOSH work. These findings are incorrect (Langer ref. 17, tab 4).

Given the lack of definitional specificity and the less rigorous analytical protocols that existed at the time (Langer ref. 17, tab 4 and National Bureau of Standards ref. 22, tab 6), the accuracy of these early reports of contamination is unclear. Petitions to require asbestos labeling on cosmetic talc were denied by the Consumer Product Safety Commission (CPSC) with the support of the Food and Drug Administration (FDA) due to concerns about the reliability of these reports (see CPSC ref. 21, tab 4). Analytical deficiencies in these reports were detailed in the National Bureau of Standards' Special Publication 506 and supporting documentation (see also Krause, et al, ref. 23, tab 4).

According to mineral scientists, the notion that asbestos is commonly found in talc ore deposits is not correct. The occurrence of asbestos in talc ore bodies is in fact rare, and is essentially limited to serpentine asbestos (chrysotile). In addition, upgrades in federal and industry talc purity standards as well as quality control procedures make asbestos contamination in talc rare to nonexistent. The Zalenski, et al, paper entitled "Talc: Occurrence, Characterization, and Consumer Applications" discusses these considerations more fully (see Zalenski, et al, ref 18, tab 4), as does the National Bureau of Standards' Special Publication 506 referenced above. If this reported contamination is of critical concern to the NTP, it is strongly encouraged to obtain additional confirmation from knowledgeable mineral scientists.

B. Asbestos was reported in Vanderbilt talc and thus poses an asbestos risk to the miners and millers of this talc as well as downstream users of this talc.

The absence of asbestos in Vanderbilt talc is discussed above. If references 10 through 15, tab 3, and ref. 16, tab 4 do not adequately confirm the absence of asbestos in this talc, we urge the NTP to review complete analytical documents which were submitted to OSHA. (A listing of all the analytical reports available to us, with basic results summarized from 1973 through 1990, are included at ref. 16, tab 3). Clarification that the minerals reported as asbestos by NIOSH (tremolite and anthophyllite) were in fact not asbestos is important since the mortality studies of upstate New York talc minors and millers are also relevant to the NTP evaluation.

The only truly fibrous or asbestiform particulate in Vanderbilt tremolitic talc (the sole producer of New York state talc since 1974) is a minor quantity of talc fiber, and to a lesser degree a very rare talc/amphibole mixed fiber. The genesis and composition of this rare mixed fiber remains undetermined after considerable study; but, it is known that these fibers are intergrown at the lattice level and can therefore not be separated. Although it has been asserted that talc fiber may be found in any talc if one looks long enough, these fibers are relatively easy to find in Vanderbilt talc. However, these fibers are still a very minor component. An analysis by weight percent of various grades showed the average highest grade % to be 0.00788 for combined talc fiber and mixed talc/amphibole fiber (Van Orden ref. 20, tab 4). In accordance with OSHA's Hazard Communication Standard and/or Asbestos Standard, such a product would not be considered asbestos-containing even if talc fiber were regulated as asbestos (which it isn't). Some of the confusion linked to the perception that asbestos exists in talc comes from the observation of these rare fibers. Health investigations involving talc fiber will be discussed below (Wylie, Mossman at ref. 25, tab 5).

It must also be recognized that if the amphibole in Vanderbilt talc (especially tremolite) was asbestos, the health effects discussed in the next section would be dramatic, since upwards of 50% of the ore and product contains these minerals. Tremolite asbestos, for example, appears to be a rather potent carcinogen, as evidenced by limited exposures to it (below a 10% content) and the prevalence of carcinogenic response associated with the mining and milling of vermiculite (Libby, Montana, see ref. 24, tab 5, pp 18-19). Animal studies also clearly reflect the elevated carcinogenic potential of tremolite asbestos (see ref. 24, tab 5, pp 22-31).

C. "Asbestos" reported in the NIOSH mortality study of Vanderbilt talc miners and millers is said to be responsible for the excess lung cancer observed in this cohort. A similar excess was observed earlier by Kleinfeld et al in miners from the same area. That is, exposure to this talc causes lung cancer.

In tab 5, we have included every health study known to us involving Vanderbilt talc. The references are preceded by a summary of these studies (Pictorial Exhibit, ref. 24 pages 42 to 47, tab 5). The animal and cellular studies include (in several cases) component concentrates (tremolite and talc fiber) tested against asbestos. Most of the studies involve epidemiological studies of our talc miners and millers. We believe that few other (if any) worker populations or mineral exposures have been studied as extensively.

Though rare, the presence of talc fiber noted in this talc may understandably be a source of concern (beyond the issue of what is and is not asbestos). In this regard, a careful review of Wylie, Mossman (ref. 25, tab 5) is helpful. In this cellular study, the authors conclude: "Our experiments also show that fibrous talc does not cause proliferation of HTE cells or cytotoxicity equivalent to asbestos in either cell type despite the fact that talc samples contain durable mineral fibers with dimensions similar to asbestos. These results are consistent with the findings of Stanton et al (1981) who found no significant increases in pleural sarcomas in rats after implantation of materials containing fibrous talc." The authors also point out the consistency of these findings with another negative tumor animal study involving Vanderbilt talc and epidemiological studies involving Vanderbilt talc (discussed below). The cellular study involved a talc fiber concentrate that is not reflective of any real world exposure known to us.

Cohort mortality studies of upstate New York talc miners and millers are also critical because they directly address human exposure and response. While animal and cellular studies involving carcinogenicity may provide a more controlled evaluation (all are negative for Vanderbilt talc – see Stanton, ref. 34 and Smith, ref. 37, tab 5 & McConnell, ref 39 tab 5), few worker populations have been as extensively studied as Vanderbilt talc miners and millers. Today, a two to threefold excess in lung cancer mortality persists in this cohort (to 1990 at least). However, more recent mortality studies of these talc miners and millers do not support a dust etiology (Delzell, ref. 26; Gamble, ref. 27; Lamm, ref. 30-31; Stille, ref. 32, in tab 5).

The causal association to tremolitic talc dust suggested by Kleinfeld (ref. 38, Tab 5) and NIOSH (Brown ref. 36, Tab 5), is not supported in subsequent, larger, more discriminating studies (Delzell, ref. 26 and Gamble, ref. 27 in particular). Today, these miners and millers are no longer considered exposed to asbestos and most agree that the observed excess lung cancer is no longer considered linked to the workplace.

Earlier mortality studies (both pro and con for a dust causal link) do suffer from many methodological shortcomings. These shortcomings include the small study population involved, the lack of dust exposure and smoking histories and proper internal controls (case - control evaluation), the lack of prior work histories and many unsupported notions which contradict

basic cause/effect principals (i.e., Hills criteria in determining causation). IARC, had only these earlier studies to cite in its review.

While it has been said that virtually all epidemiological efforts have shortcomings, the most recent work by Delzell and Gamble strive to address earlier study weaknesses. In both studies, the researchers conclude that the excess lung cancer observed is unlikely linked to the dust exposure principally because they demonstrated that smoking could account for the excess and there is no dose response relationship demonstrated. In fact, the latter is inverse in relation to observed nonmalignant respiratory disease mortality. The frequently referenced NIOSH study merely recorded the excess lung cancer, incorrectly found "asbestos" where it did not exist and concluded that this "asbestos" was the logical cause of the excess. Although time from first exposure to death did support a causal link, other key causality considerations were not properly addressed (smoking history, exposure by either tenure or dust levels, consistency with other findings, etc.). References 40 through 47 and 49 to 51, tab 6 contain critiques which address several of the cohort studies (principally the Brown, et al, NIOSH study). These critiques (the Gamble critique in particular – ref. 40, tab 6) provide compelling criticism of the NIOSH work.

Reference 33, tab 5 reflects a mortality study of Vanderbilt talc users ("population at risk") underwritten by the National Paint and Coatings Association (NPCA) and published in 1981. This study finds no excess pulmonary cancer in over 16,000 paint workers from 32 plants in the United States. A cover sheet attached to this reference explains the very high use of Vanderbilt talc in the paint industry (which persists to this day).

At present, the predominant use of Vanderbilt talc is in paint manufacturing. Ceramic use has dramatically declined due to process upgrades in the ceramics industry allowing for the use of cheaper raw materials. There are no other Vanderbilt talc user health studies known to us. One pottery worker study referenced by NTP in support of it's review of pure talc (Thomas, et al) suggests excess lung cancer among workers exposed to pure talc (among other things) but not among a subpopulation of these pottery workers earlier exposed to tremolitic talc (origin of the talc unclear). This study gives no support to a link between tremolitic talc and cancer.

It can reasonably be assumed that few if any downstream users of tremolitic talc would experience dust exposures greater than those experienced by our own miners and millers. If cancer can not be demonstrated in Vanderbilt talc miners and millers, or in direct animal testing involving this talc, a significant cancer risk to downstream users is difficult to imagine.

While Vanderbilt talc should not be viewed as asbestos containing or cancer causing, there is no question that overexposure to this tremolitic talc (or any mineral dust) can result in nonmalignant respiratory disease. We believe that exposure to all talc has been reasonably linked to the development of pleural plaques and we have seen this in our own talc workers. There is no clear evidence, however, that pleural plaques promote the evolution of pleural tumors or even pulmonary impairment such as diminished pulmonary function (Boehlecke ref. 52, tab 7).

Reference 52, tab 7 contains comments submitted to the OSHA docket (1990) concerning the regulation of nonasbestiform amphiboles by Brian Boehlecke M.D. Dr. Boehlecke is a pulmonary consultant who has reviewed the pulmonary condition of Vanderbilt miners and millers over the last eighteen years. We agree with Dr. Boehlecke's observations regarding pleural plaques and parenchymal pneumoconiosis ("talcosis"). Dr. Boehlecke has reviewed numerous talc studies and offers some comparative comments regarding the prevalence and type of pulmonary abnormalities noted in tremolitic talc workers contrasted to nontremolitic talc workers. A review of this reference is highly recommended. The current pulmonary status is consistent with those reported by Dr. Boehlecke in 1990.

An interesting study was conducted in the mid 1980's by Dr. Steven Lamm during a follow-up cohort study. In this study, Dr. Lamm compared rates for lung cancer deaths and pneumoconiosis for Vanderbilt talc workers (said to be exposed to asbestos by NIOSH) and Vermont talc workers (said not to be exposed to asbestos by NIOSH) with at least one year of exposure. Cohort comparisons of this sort can be problematic for many reasons, but these groups did share many similarities (the cohort size was approximately similar, the years of exposure were similar, overall dust levels were similar, quartz exposure (trace) was similar in both dusts, etc.). In this comparison, the lung cancer rate was essentially the same and the rate for nonmalignant respiratory disease was slightly higher in the Vermont cohort. This comparison can be further reviewed in reference 31, tab 5 in a preliminary report entitled "Absence of Lung Cancer Risk from Exposure to Tremolitic Talc" February 14, 1986 pages 21 through 23.

While nonmalignant respiratory disease and other abnormalities linked to talc are not the subject of this NTP evaluation, we have addressed them because of the mistaken assumption by some that such abnormalities are only linked to asbestos or are a precursor to pleural cancers (i.e., mesothelioma).

D. Cases of malignant pleural mesothelioma have been reported for individuals exposed to tremolitic talc mining and milling.

This IARC reference is problematic. In the most recent cohort follow-up (Delzell, 1995 – ref 26, Tab 5), two mesothelioma cases were reported, but neither was considered linked to talc exposure. The first case was reported by NIOSH (Brown et al ref. 36, Tab 5) and was also discounted because the latency was too short (diagnosed 15 years after first talc exposure). The second case died in 1986 and worked 6 months at the mine in the Engineering office as a surveyor in 1948. After this brief encounter in 1948, he then worked many years repairing home heating systems.

Four case studies are referenced in the IARC supplement (Vianna, et al) but are not sufficiently detailed in the text to determined if the case referenced in the NIOSH study was included. The other cases, unknown to us, may have involved exposures in other area mines (no longer in operation), may have been linked to other asbestos exposures or may have been misdiagnosed. It appears that the 1981 paper studied the general population in selected New

York State counties and was not specific to talc mining in the region. Interpretive problems associated with case study reports are well understood and frequently render such reports anecdotal at best. In addition, given experience with actual asbestos exposure (especially asbestos amphibole exposure), adequate latency in the Vanderbilt cohort could have reflected cases which would show an association by the end of 1989 (vital status cut off of the latest study) - although a latency beyond 40 years would be preferable.

There is much controversy regarding the cause and ("mis") diagnosis of mesothelioma, and the NTP panel members are no doubt familiar with these issues. Tab 8 contains relevant papers which address these problems. Given the status of available data on mesothelioma in general and Vanderbilt talc specifically, one cannot reasonably conclude that a cancer association exists.

In summary, if a review of "talc containing asbestos" or "talc containing asbestiform fibers" is undertaken, we request that the NTP recognize the shortcomings of the 1987 IARC Supplement and evaluate the category based upon all available studies and documentation. Considerable confusion obviously exists in this area. The unfortunate link between talc and asbestos has been highly publicized and tends to be an emotional issue. Moreover, some groups (i.e. NIOSH) have taken strong positions (especially regarding Vanderbilt talc) and objectivity may be challenged. For these reasons we believe that it is of particular importance that the weight of all available evidence be carefully considered. The NTP has an opportunity to help correct past errors, misperceptions and unsupported findings. We hope it will take advantage of this opportunity.

Respectfully submitted,

R.T. VANDERBILT COMPANY, INC.

By: John W. Kelse

John W. Kelse
Corporate Industrial Hygienist,
Manager Occupational Health & Safety
and Responsible Care® Coordinator

REFERENCES

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R.T. Vanderbilt Company, Inc.
INDUSTRIAL MINERALS AND CHEMICALS

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July 8, 2002

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, North Carolina 27709

RE: Tenth Report on Carcinogens (RoC) Nomination:
"Talc – Asbestiform and Non-Asbestiform"

Dear Dr. Jameson:

In correspondence dated July 9, 2001 from Dr. Olden (appended), the captioned nomination was deferred from listing in the 10th RoC pending further review. Dr. Olden requested that additional information on this nomination be submitted.

This correspondence provides additional information in regard to the ***asbestiform*** portion of the nomination. As pointed out in my original submission, this entry essentially refers to a single talc product, a unique industrial grade talc mined and milled by the R. T. Vanderbilt Company Inc. Hence, all health information pertaining to the miners and millers of this talc is of critical significance to this nomination.

Appended to this correspondence is the most recent mortality study of these talc miners and millers as well as a separate exposure assessment manuscript linked to this study. Both papers have been approved for publication in the Annals of Occupational Hygiene (confirmation is appended to the manuscripts). Although this work had been peer reviewed and provided to the NTP during the original comment period, it had not been submitted for publication at that time. The Board of Scientific Counselors RoC Subcommittee excluded this study from its deliberations because it had not been approved for publication.

The second submission is a public comment transcript submitted to the Mine Safety and Health Administration concerning a Notice of Proposed Rule on revisions to their asbestos standard. These comments summarize the current health status of these same New York State miners and millers and includes a summary of our most recent medical surveillance findings. Slides used in that oral presentation are enclosed as well.

During the original NTP public comment period, substantial written and oral comments were provided. This record greatly expanded and clarified a variety of contested points in the NTPs original background document.

Beyond the appended submissions, I would respectfully suggest that the NTP carefully, dispassionately and fully review all the submissions previously provided on both talc nominations. I believe this extensive record more than adequately reflects a science base that does not support further listing consideration for either talc nomination.

Sincerely yours,

R. T. VANDERBILT COMPANY, INC.

John W. Kelse

John W. Kelse, Corporate Industrial Hygienist
Manager, Corporate Risk Management Dept.

11/26/86

U.S. DEPARTMENT OF LABOR
OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION
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MICROSCOPY BRANCH
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Dr. Greg Piacitelli
Department of Health & Human Services
NIOSH-ALOSH
944 Chestnut Ridge Road
Morgantown, WV 26505-2888

Dear Greg,

I have enclosed xerographic copies of all the organized work I could find that was not directly involved with compliance actions. Of course, the color photos don't give you a great deal of information in black and white. The captions underneath them will in some cases give some interesting insight. Probably the most interesting features are demonstrated by the high resolution electron micrographs. These show typical industrial talcs and anthophyllite. Anthophyllite shows major regularity and fairly constant double chain structure typical of amphiboles. The fibers seen in the industrial talc show a great disorder. The only major regularity is the 9 angstrom repeat from partial 1-tuple unit to the next. It is probably here in this feature that the discrepancies found in other analyses are born. It is only by a combined optical/electron optical approach can the nature of the intermediate fibers be determined. Even at that, they defy definite description.

In general, the Vanderbilt products that we have examined contain the minerals stated in the MSDS's. The controversy emerges when mineralogical definitions are or are not applied to the particles resulting after the material has been crushed to the final material. Asbestos as a mineralogical term applies to fibers of a mineral which grew naturally that way. As a legal term it has come to mean any particle which is three time longer than it is wide. This rule applies equally to chrysotile and dimension lumber. The minerals present in industrial talcs especially tremolite and anthophyllite as they currently are found are not mineralogically fibrous for the most part. They are not "asbestos" mineralogically speaking. These minerals are members of a group of similar minerals called the amphibole family. Amphiboles as well as other minerals tend not to occur in the same habit (crystal growth pattern) all of the time. That is, sometimes a mineral will be a fiber, sometimes it will be acicular, sometimes tabular sometimes massive; depending on where and under what conditions the mineral crystallized. It is in every case still essentially the same mineral. Sometimes, different names have been given to the various habits. (e.g. riebeckite = massive and crocidolite = fibrous varieties of the same mineral). For some minerals the same name applies regardless the habit. Specifically, this is the case for three of the minerals covered under the OSHA asbestos standard: tremolite, actinolite and anthophyllite.

Materials tend to break along the directions of least resistance to parting. In the amphiboles, there is a direction along which there is very little resistance to parting compared with other directions in the crystal. This direction happens to be parallel to the direction of growth in the

asbestos varieties of the same mineral. When crushed, easy parting leads to particles of mineral which are elongated. In phase contrast microscopy, for particles less than about 1 micrometer in diameter, a differentiation whether or not an individual particle is mineralogically asbestos is not possible in general. The morphology for most larger particles is usually sufficiently distinct that a determination can be made. These particles are much more blunt, lacking the "bundle of sticks" effect, lacking splintered ends etc. In large ensembles of particles from asbestos vs non-asbestos forms it is possible to derive differences in the average aspect ratio or in the direction of repose in zero degree selected area diffraction patterns. It is not wise to consistently apply these tests on individual fibers.

The above discussion applies to the tremolite and anthophyllite that is present in the products. Please do not get lost in the technical nature of that discussion. It tends to obscure some really startling observations. When one looks at the industrial talcs in the microscope, he sees large numbers of particles that are much longer than 20 to 1 even to nearly 100 to 1 in aspect ratio. The first reaction is to say these are the asbestos fibers of tremolite and anthophyllite indicated by the known presence of those minerals in the products. Unfortunately, this is a false assumption. They are for the most part fibers of industrial talc. They have been dubbed intermediates by us, as talcboles by Malcom Ross and fibrous biopyriboles by David Veblen. What they are not is anthophyllite or tremolite.

Polarized light microscopy has shown these fibers to have indices of

refraction in the range for talc (dispersion staining). They have been shown to have an average maximum angle of extinction of approximately 11 degrees compared with 0 degrees for anthophyllite and 17-22 degrees for tremolite. More surprising still are some fibers that on one end have dispersion colors for anthophyllite and on the other end colors consistent with talc. Light microscopy tends to eliminate these fibers as one of the minerals covered by the OSHA standard. Compare this with what we find for electron microscopy.

Standard analysis of these materials by electron microscopy shows that the same fibers we called non-anthophyllite by light microscopy should be called anthophyllite. Semi-quantitative chemistry and selected area diffraction based on layer-line measurement or rough indexing matches anthophyllite. The fibers seen do show splintering, do show elongated aspect ratio. By electron microscopy alone, it should be concluded that the fibers are indeed anthophyllite. There is an error of logic here.

It is usually assumed that all there is present are the minerals stated in the MSDS or by private x-ray diffraction. The fault can be corrected when the analyst realizes that in this particular mineral, the deposit was anthophyllite at one time. Nature has begun transforming this deposit to the mineral talc. The particular mechanics of this are beyond the scope of this letter. Suffice it to say that it is being done in such a way as to leave the more major structure of the anthophyllite fibers intact while transforming them to talc. This residual structure has given rise to electron diffraction patterns that mimic amphibole patterns. Very careful measurement

and calibration of these patterns reveal subtle strains in the structure leading to a mineral with similar features to talc and to anthophyllite and yet the numbers fall in between. Energy dispersive analysis by X-rays (EDX) shows a similar result. Both talc and anthophyllite have a magnesium silicate structure. Anthophyllite has 7 magnesium or magnesium replacing atoms for every 8 silicon or silicon replacing atoms. For talc the ratio is 6 Mg to 8 Si when appropriately normalized. This is a very small difference to try to quantify. Most laboratories don't try. We looked at an ensemble of known anthophyllite fibers and an ensemble of known talc particles. From the data thus obtained, we were able to show that the fibers found in the Vanderbilt talcs we looked at were mostly in the range between talc and anthophyllite. As a side note, there was insufficient calcium found in any of the very fibrous particles to allow the tentative identification of tremolite such as has been offered by some groups. We found an average of approximately 0.2 atomic units per 8 silicon atoms. This is lower than the 1.34 atoms required by the definitions accepted by the American Mineralogical Society.

In order to elucidate the structure, we then began to look at fibers of the material with High resolution electron microscopy. I have included with this letter some copies of representative photographs. The truth of the intermediate nature for these fibers is immediately apparent. The photos of the standard anthophyllite fibers show a mostly regular pattern of "double-chain" repeats. (The small spots are believed to be silicon atom positions in these photos). The double chain consists of one bright line with one lesser line. Please study these photos in comparison to those provided

for the industrial talc fibers. Note that there is a great irregularity to these patterns. There are some areas where an amphibole pattern is observed. There are areas where a broader expanse of single chains occur and other places where there are n-tuple chains. There is no long range order here. Note however, that the long chains are all about 9 angstroms apart regardless whether they are part of a double chain, single or a multiple construct.

I have described these other fibers because they are the fibers with the closest morphological similarity to asbestos. They do have splintering and bundle of sticks and frayed ends as characteristics. These are characteristics which we often ascribe to truly asbestiform minerals. All the samples we have examined have been crushed prior to our receiving them. Therefore, we cannot say whether they grew in nature as asbestos fibers. They do look like asbestos and if morphology is the major role in toxicity or carcinogenicity these should be considered more important that the non-fibrous cleavage fragments of tremolite or anthophyllite. My purpose is not to discuss epidemiology but rather give a short explanation of some of the conclusions we have come to from years of studying the mineralogy and microscopical properties of Vanderbilt fibers. I conclude by stating simply that all the products we have investigated have shown elongated cleavage fragments of tremolite and anthophyllite having aspect ratios in excess of 3:1. We have found, in addition, a class of fiber present in the products which is intermediate in nature between talc and anthophyllite. In investigating these we have seen on occasion a fiber that would be called anthophyllite. Notwithstanding this, the bulk of truly fibrous particles fall

into this intermediate class.

There is much more that could be said about what we have found but this letter should cover the major points. Should you have any questions or wish to discuss it further, I am at your service.

Sincerely,

11-26-84

Daniel T. Crane
Supervisory Physical Scientist
Microscopy Branch

cc Amanda Edens (OSHA)

R.T. Vanderbilt Company, Inc.

INDUSTRIAL MINERALS AND CHEMICALS

Material Safety Data Sheet

minusa

Section I. Chemical Product and Company Identification

Product Name/ Trade Name	**NYTAL® 400**	**Code**	31209
		CAS#	Mixture
Supplier	R. T. VANDERBILT COMPANY, INCORPORATED 30 WINFIELD STREET NORWALK, CT 06855	**In case of Emergency**	(203) 853-1400
Synonym	Industrial talc, tremolitic talc	**Protective Clothing**	
Chemical Name	Hydrous calcium magnesium silicate mineral mixture		
Chemical Family	Phylosilicates (structural).		
Manufacturer	R. T. Vanderbilt Company, Inc. 30 Winfield Street Norwalk, CT 06855	**Material Uses**	Additive in paints and ceramics

Section II. Composition and Information on Ingredients

Name	CAS #	% by Weight	TLV/PEL
tremolite (nonasbestiform)	14567-73-8	30-50	As particles not otherwise regulated (PNOR).
talc	14807-96-6	20-40	TWA 2 mg/m³ from respirable fraction (ACGIH) See Section XVI (OSHA)
serpentine (antigorite, lizardite)	12135-86-3	20-30	As particles not otherwise regulated (PNOR).
anthophyllite (nonasbestiform)	17068-78-9	2-10	As particles not otherwise regulated (PNOR).
quartz	14808-60-7	0.32	OSHA PEL: TWA respirable fraction formula: 10 mg/m³ / % SiO_2 +2 ACGIH: TWA 0.05 mg/m³ from respirable fraction
Total Product			TWA: 15 mg/m³ total dust 5 mg/m³ respirable dust (OSHA) As particles not otherwise regulated (PNOR).

Section III. Hazards Identification

Emergency Overview	Not an acute hazard. Contains quartz. May cause mechanical eye or skin irritation in high concentrations. As with all mineral spills, minimize dusting during clean-up. Do not breathe dust. Prolonged inhalation may cause lung injury. Product can become slippery when wet.
Target Organs	Pulmonary System (chronic risk).

Continued on Next Page

Section IV. First Aid Measures

Eye Contact	Flush with plenty of flowing water. Get medical attention if irritation persists.
Skin Contact	Wash off with water.
Inhalation	Allow the victim to rest in a well ventilated area if high concentration is inhaled and mechanical irritation or discomfort occurs. Seek medical attention if irritation persists.
Ingestion	Unlikely to be toxic by ingestion.

Section V. Fire and Explosion Data

Flammability of the Product	Non-flammable.
Auto-Ignition Temperature	Not applicable.
Flash Points	Not applicable.
Flammable Limits	Not applicable.
Products of Combustion	Not applicable.
Fire Hazards in Presence of Various Substances	Not considered to be flammable.
Explosion Hazards in Presence of Various Substances	None.
Fire Fighting Media and Instructions	Product will not burn, use appropriate extinguishing media for surrounding fires.
Special Remarks on Fire Hazards	Not available.
Special Remarks on Explosion Hazards	Not available.

Section VI. Accidental Release Measures

Small Spill	Use a vacuum to clean up spillage. If appropriate, use gentle water spray to wet down and minimize dust generation. Place in a sealed container. Material will become slippery when wet.
Large Spill	Use a shovel to put the material into a convenient waste disposal container. Finish cleaning by spreading water on the contaminated surface and allow to evacuate through the sanitary system. Avoid excessive dust generation. Use respiratory protection in high dust conditions.

Section VII. Handling and Storage

Handling and Storage Procedures	No special storage considerations. Handle in ways which minimize dust generation.

Continued on Next Page

Section VIII. Exposure Controls/Personal Protection

Engineering Controls	Use process enclosures, local exhaust ventilation, or other engineering controls to keep airborne levels below recommended exposure limits. If local exhaust ventilation is used, a capture velocity of 150-200 fpm is recommended.
Personal Protection	Safety glasses. Any NIOSH approved filler dust respirator. No special skin protection required. Wash skin if mechanical irritation is experienced.

Section IX. Physical and Chemical Properties

Appearance	White powder
Molecular Weight	Not available.
pH	Not available
Melting/ Sublimation Point	Not available.
Specific Gravity	2.85 (Water = 1)
Volatility	Non-volatile.
Odor	None
Solubility	Insoluble in cold water.

Section X. Stability and Reactivity Data

Stability	The product is stable.
Instability Temperature	Not applicable
Conditions of Instability	None known
Incompatibility with Various Substances	Non reactive.
Corrosivity	Not available.

Section XI. Toxicological Information

Routes of Entry	Inhalation. Ingestion.
Acute Effects	
Eye contact	Not a primary eye irritant. May cause mechanical irritation,
Skin contact	Mechanical skin irritation is possible but unlikely. Not absorbed through skin. Possible granuloma formation in open wounds (requires repeated, massive applications).
Sensitization	Not a sensitizer.
Ingestion	Not an ingestion hazard.
Inhalation	Inhalation of high concentrations may cause mechanical irritation and discomfort. Repeated exposure may cause chronic effects.

Continued on Next Page

Remarks	No additional remark.
Chronic Effects	**CARCINOGENIC EFFECTS**: See remarks. **MUTAGENIC EFFECTS**: None known. **TERATOGENIC EFFECTS**: None known. **DEVELOPMENTAL TOXICITY**: None known.
Remarks	TALC: Prolonged exposure to excessive airborne concentrations of talc can result in scarring of the lungs (pneumoconiosis) or of the covering of the lungs (pleural thickening). Pneumoconiosis may produce symptoms of cough or shortness of breath. Pleural thickening usually produces no symptoms. Conditions can be determined by chest radiographic examination and pulmonary function test (FEV and FVC). Bronchial irritation may cause sputum production. CRYSTALLINE SILICA: Overexposure to respirable crystalline silica dust can cause silicosis, a form of progressive pulmonary fibrosis. "Inhalable" crystalline silica (quartz) is listed by IARC as a Group I carcinogen (lung) based on "sufficient evidence" in occupationally exposed humans and sufficient evidence in animals. Crystalline silica is also listed by the NTP as a known human carcinogen. Some studies have not demonstrated a cancer association and considerable controversy exists concerning the IARC and NTP classification. New York State talc has been tested as a whole and in parts in several animal studies with no carcinogenic association demonstrated. Epidemiologic studies in humans have been interpreted in conflicting ways with no clear evidence of an increased risk in lung tumors in association with exposure. Human, animal and in-vitro tests of basic product ingredients (talc and nonasbestiform tremolite) do not show a carcinogenic effect. All tremolite is of the nonasbestiform, common cleavage fragment variety. Excessive exposure to any dust may aggravate pre-existing respiratory conditions.

Section XII. Ecological Information

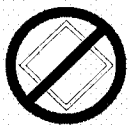
Ecotoxicity	None known.
BOD5 and COD	Not available.
Products of Biodegradation	None known.
Toxicity of the Products of Biodegradation	None known.
Special Remarks on the Products of Biodegradation	Not available.

Section XIII. Disposal Considerations

Waste Information	Not a US RCRA hazardous waste. Dispose of in accordance with state and local regulations.

Section XIV. Transport Information

DOT	Not a DOT controlled material (United States).



Not applicable.

Maritime Transportation	Not available.

Continued on Next Page

Section XV. Other Regulatory Information and Pictograms

TSCA

Listed.

Federal and State Regulations

OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200).

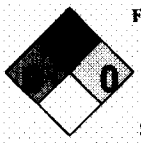
California prop. 65: This product contains the following ingredients for which the State of California has found to cause cancer which would require a warning under the statute: quartz
Pennsylvania RTK: talc; anthophyllite (nonasbestiform); quartz
Florida: tremolite (nonasbestiform); talc; quartz
Minnesota: talc; quartz
Massachusetts RTK: talc; quartz
TSCA 8(b) inventory: NYTAL® 400

Hazardous Material Information System (U.S.A.)

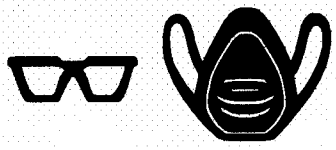
Health Hazard *	1
Fire Hazard	0
Reactivity	0
Personal Protection	E

* Chronic Potential

National Fire Protection Association (U.S.A.)



Protective Clothing (Pictograms)



Section XVI. Other Information

References

Not available.

Other Special Considerations

Quartz (none detected to less than 1.0% - this quartz range is "typical" and may change slightly with different lots.)

Numerous samples for airborne concentrations of free silica during talc processing consistently reflect free silica levels in the <0.05 mg/m3 range (if detected at all).

Talc PEL: The current OSHA PEL remains 20 mppfc. Due to antiquated particle counting technique, the gravimetric (ACGIH) limit is recommended.

Validated by Sue Kelly on 6/20/2002.

Verified by Sue Kelly.

Printed 7/5/2002.

Information Contact **John Kelse (203) 853-1400 ext. 217**
Corporate Risk Management

UAB SCHOOL OF PUBLIC HEALTH

Department of Epidemiology

November 29, 2000

Dr. Mary S. Wolfe, Executive Secretary
NIEHS Mail Drop A3-07
111 TW Alexander Drive, Room A-329
Bldg 101 South Campus
Research Triangle Park, NC 27709

Re: 10th ROC Nominations: Solicitation of Public Comment—"Talc Containing Asbestiform Fibers"

In response to the referenced call for public comment, we are submitting herein written comments and are enclosing a copy of a report entitled, "Retrospective Follow-up Study of Mortality Patterns among Gouverneur Talc Company Workers." The report, which we issued in 1995, received peer review by several scientists. We are preparing two papers for publication based on the report and plan to submit the papers to a journal in January 2001.

The enclosed report describes the most recent analysis of mortality patterns among Gouverneur Talc Company (GTC) workers, a group that has been studied extensively over the past three decades. The report provides information related to the potential carcinogenicity of talc. We intend that this submission be considered by the National Toxicology Program (NTP) Board of Scientific Counselors' Subcommittee prior to the scheduled meeting on December 13-15, 2000.

Our study extended the follow-up period of previous investigations through the end of 1989 and incorporated several other improvements over previous research on GTC workers. In particular, our research:

- used, in addition to the United States general population, state and regional comparison groups;
- evaluated cause-specific mortality patterns by duration of employment and by time since first employment;
- estimated workers' quantitative exposure to total respirable dust; and
- analyzed lung cancer and nonmalignant respiratory disease mortality rates by estimated cumulative respirable dust exposure, using an internal referent group; these latter analyses reduce the possibility that results are due to confounding or observation bias.

Our study found that GTC workers, compared to the regional general population, had 2.3 times more than expected deaths from lung cancer (31 observed/13 expected deaths) and 2.2 times more than expected deaths from nonmalignant respiratory disease (28 observed/13 expected deaths). The lung cancer excess was concentrated in short-term employees and in underground

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miners. Millers, whose exposure to respriable dust was similar to that of underground miners, had only a small, statistically nonsignificant increase in lung cancer deaths. There was no, or an inverse, relation between cumulative respirable dust levels and lung cancer.

In contrast, an excess of nonmalignant respiratory disease deaths occurred both in short-term and in long-term workers and both in miners and in millers, and workers with cumulative dust exposure above the median had a higher mortality rate than other workers. In particular, decedents with pneumoconiosis or interstitial lung disease had median durations of employment and cumulative respirable dust exposure that were seven and 13 times higher, respectively, than the overall group of GTC workers.

We agree with the NTP that GTC workers clearly have increased mortality from lung cancer. However, several of our results argue against exposure to dust in GTC operations as the cause of the lung cancer excess:

- The lung cancer excess was concentrated in short-term workers, even when analyses were restricted to the employee subgroup with 20 or more years since hire (i.e., the subgroup with long induction time) (see our report, table III-8).
- The lung cancer excess was concentrated among underground miners (18 observed/4.1 expected, SMR=440, 95% CI=261-695), whereas millers, a group with estimated high exposure to dust, had an SMR for lung cancer of only 139 (7 observed/5.0 expected; 95% CI=56-287). Further, workers classified as unexposed to talc had a nonstatistically significant threefold increase in observed over expected lung cancer deaths (3 observed/0.97 expected, SMR=309, 95% CI=62-903) (see our report, table III-13).
- Lung cancer decedents had low estimated cumulative respirable dust exposure (median=297 mg/m^3-days) compared to the overall group of GTC workers (median=428 mg/m^3-days) (see our report, page 67 and table III-17), and cumulative respirable dust exposure levels were unrelated, or even inversely related, to lung cancer mortality rates (see our report, table III-16).

The lack of a dose-response gradient for estimated respirable dust exposure and lung cancer mortality rate ratios, along with the other results mentioned above, suggest that the overall increase in GTC workers is due, at least in part, to factors other than talc dust. The results do not support an interpretation that the talc dust in GTC operations is *per se* a lung carcinogen.

The NTP Review Group appears to have relied heavily on previous studies of GTC workers in determining if talc containing asbestiform particles is a human carcinogen. In reaching a final determination, we hope that the group will recognize that the various studies should not be considered as providing independent information on this topic. If, as several authors have suggested, the elevated lung cancer rate among GTC workers is due to an unidentified confounder (e.g., smoking, radon, other employment), the same confounder is likely to produce spurious results in all analyses of GTC employees, irrespective of the amount of follow-up time. Studies of truly independent groups (i.e., in Vermont and Norway), like studies of GTC workers,

have yielded inconclusive evidence that talc ore dust is a lung carcinogen. In particular, the Vermont study, like our GTC study, found that the respiratory cancer excess was restricted to miners and did not affect millers and suggests that some feature of the mine environment rather than talc ore dust is implicated.

Thank you for the opportunity to add to the information about disease patterns among people exposed to talc being considered by the NTP.

Yours sincerely,

E Delzell

Elizabeth Delzell, SD

Kent Oestenstad

Kent Oestenstad, PhD

Written Comment on 10th ROC Nomination on
Talc Containing Asbestiform Fibers

For the
NTP Board of Scientific Counselors" Subcommittee Meeting
December 13, 14, 15, 2000

Submitted by
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SUMMARY

NTP has determined that talc containing asbestiform fibers is known (RGI Review) or reasonably anticipated (RG2) to be a human carcinogen. This determination is based on (moderate) increases in lung cancer and mesothelioma mortality among talc miners and millers. The epidemiology studies cited to support these determinations are (Kleinfeld et al, 1974; Brown et al, 1979; Dement et al, 1980; Lamm et al, 1988).

Such a determination is **not** supported by the weight of evidence, and NTP has not presented a scientifically credible argument to support this classification. For example, the studies cited by NTP have been superseded by more relevant studies with more cases, longer follow-up, analyses by exposure and adjustments for confounding (Brown et al, 1990; Gamble, 1993; Delzell et al, 1995). Two of these studies were not even cited in the documentation. The rationale for opposing the NTP classification is based, in part, on the following arguments.

1.) NTP should provide a functional definition of asbestiform fibers, and clearly demonstrate that Vanderbilt talc (and NY talc as in the study by Kleinfeld et al, 1974) contains asbestiform fibers.

NTP does not provide an accurate description of the mineralogy of Vanderbilt talc in terms of cleavage fragments, asbestiform fibers, talc fibers, and asbestos. The undemonstrated presumption that Vanderbilt talc is the same as asbestos results in an expectation bias (similar to diagnostic bias) that colors (biases) the interpretation of the evidence.

2.) NTP should clearly indicate how the evidence meets the standards for assuming there is a causal association between increased risk of lung cancer and exposure to Vanderbilt talc.

The observed increases in lung cancer from mortality studies of Vanderbilt workers could be due to confounding and chance, the weight of the evidence is not consistent with a causal association, and the classification of Vanderbilt talc as a carcinogen is not supported by the data.

a) There is no gradient for the risk of lung cancer to increase with increasing years worked or increased exposure to Vanderbilt talc. This is strong evidence against a causal association.

Risk ratios with increasing exposure to Vanderbilt Talc (internal comparisons)

Cumulative Exposure	0-62 mg/m3-years	63-325 mg/m3-yrs	326-1704 mg/m3-y	1705+
Delzell et al (1995)	1.00 (referent)	0.74 (0.27-2.1)	0.68 (0.24-1.9)	0.45 (0.17-1.2)
Tenure	< 5 yrs tenure	5-15 years tenure	15-36 years tenure	
Gamble (1993) (smokers compared to smokers)	1.00 (referent)	0.50 (0.05-4.98)	1.00 (0.28-3.59)	

b) Weak associations in high exposure groups with > 20 years latency detracts from a causal association, as the risk could be due to confounding (e.g. smoking) and chance.

SMRs of Vanderbilt workers with 20 or more years latency and long tenure

Brown et al (1990)	20-36 years exposure	1.82 (0.21-6.36)
Delzell et al (1995)	5 or more years exposure	2.15 (0.86-4.42)

Strong associations in short-term workers with 20 years latency are consistent with confounding exposures. Short-term Vanderbilt workers should be at least risk if talc is a carcinogen. These associations are unlikely to be due to chance and are not coherent with a causal association.

SMRs of Vanderbilt workers with 20 or more years latency and short tenure

Brown et al (1990)	1 year or less exposure	3.64 (1.54-7.04)
Delzell et al (1995)	Less than 5 years exposure	3.71 (2.23-5.80)

c) The temporal relationships of lung cancer and exposure are more coherent with a smoking etiology than a talc exposure etiology. The latency from beginning smoking to lung cancer death is similar to that found in populations of smokers. The latency from hire date to lung cancer death is shorter than the latency for highly exposed asbestos workers, and is therefore biologically implausible.

Latencies for lung cancer attributable to smoking and asbestos compared to latencies for smoking and talc exposure for Vanderbilt lung cancer cases.

	Latency since beginning smoking		Latency for Exposures at Work	
	Liddell (1980); Wynder (1977)	Vanderbilt workers Gamble (1993)	Hi levels Asbestos: Selikoff, Dement	Vanderbilt Talc Gamble (1993)
Years latency	About 40 years	40 years	28-34 years	25 years

Does the weight of the evidence from studies of Vanderbilt workers support or detract from the hypothesis that there is a causal association between talc exposure and risk of lung cancer, and that Vanderbilt talc should be considered a carcinogen?

The evidence detracts from the hypothesis of a causal association:

+ There is no exposure-response trend.
+ The association in high exposed workers with adequate latency is weak, is not statistically significant and could be due in part or in whole to cigarette smoking.
+ The association is strong and statistically significant only in short-term workers with minimal exposure but long latency and there is evidence against very high exposures in their short employment.
+ The temporal relationships are coherent with a smoking etiology, and inconsistent with a talc exposure etiology.

INTRODUCTION

NTP has determined that talc containing asbestiform fibers is known (RGI Review) or reasonably anticipated (RG2) to be a human carcinogen. This determination is based on (moderate) increases in lung cancer and mesothelioma mortality among talc miners and millers. The studies cited to support these determinations are (Kleinfeld et al, 1974; Brown et al, 1979; Dement et al, 1980; Lamm et al, 1988).

Unfortunately, NTP does not provide the rationale that these increases in mortality constitute causal associations. The 1964 Surgeon Generals Report on smoking and lung cancer provides an early example on how a science-based determination of causality should be conducted. Such an approach is a generally accepted requirement in epidemiology in making determinations of the carcinogenicity of any substance.

The evidence cited by NTP is incomplete as appropriate studies are not part of the documentation, similar studies are inappropriately counted more than once, and the standards for determining causality are not supported by the evidence. Thus, the basis for their conclusion is of necessity hidden in speculation. I will outline causal criteria and suggest the weight of the epidemiologic evidence does not satisfy these criteria, and the evidence does not support the conclusion of NTP.

ASBESTIFORM TALC: What is it? What is the evidence that Vanderbilt talc contains asbestiform fibers? What is the evidence that asbestiform talc is a surrogate for asbestos? (Vanderbilt talc is the term used to describe the talc at issue since all the epidemiology studies are of Vanderbilt workers with the exception of Kleinfeld et al (1974).

The case has not been made that Vanderbilt talc contains asbestiform fibers.

A primary issue in the carcinogenic classification of asbestiform talc is a correct definition and characterization of the product being labeled. The product "talc containing asbestiform fibers" must be correctly described and the evidence presented making the case that Vanderbilt talc actually contains "asbestiform fibers" in sufficient quantities to be so characterized. If experimental evidence of asbestos studies is included to assess biological plausibility, then it is essential that all the evidence for and against the similarity of asbestos and Vanderbilt talc be presented.

An adequate description of Vanderbilt talc has not been provided sufficient to demonstrate that it is a "surrogate of asbestos." There is little to no discussion of particle dimensions, aspect ratios, regulatory versus mineralogical definitions, asbestiform versus nonasbestiform habits of minerals. NTP uses the descriptions of Vanderbilt talc found in Dement and Zumwalde (1979), but does not cite more complete descriptions that are inconsistent with those used by NTP. For example, Campbell et al (1979) visually show the differences between nonasbestiform tremolite (called blocky, acicular and fibrous tremolite) compared to tremolite asbestos. Approximately 50 percent of particles in fibrous tremolite were regulatory fibers (length 5 um or more, diameter 3 um or less, aspect ratio 3:1 or greater), but there were no particles with the very high aspect ratios (> 50:1) and small diameter characteristics of tremolite asbestos. The long, thin, durable fibers characteristic of tremolite asbestos that range upward to several hundred um or longer in length and diameters ranging down to 0.1-0.2 um in diameter were not observed in the samples of nonasbestiform tremolite. About 35% of regulatory fibers in tremolite asbestos have aspect ratios greater than 20:1, and about 60% greater than 10:1. Fibrous nonasbestiform tremolite had less than 1% (1 fiber out of 200) with an aspect ratio > 20:1 and 6% greater than 10:1. Unfortunately the description of Vanderbilt talc cited by NTP (Dement and Zumwalde, 1979) does not provide the distribution of fibers by aspect ratio. Kelse and Thompson (1989) demonstrated that the amphibole particles found in Vanderbilt talc do not show the characteristic long thin fibers of tremolite asbestos, and so by this criteria would not be classified as talc containing asbestiform fibers.

To incorrectly label a product as asbestos (or a surrogate of asbestos) can result in an expectation bias in the interpretation of study results. Expectation bias is analogous to diagnostic suspicion bias, where knowledge (or in this case incorrect knowledge) of occupation or exposure may influence the diagnosis and /or the search for a putative cause (Sackett, 1979; Gamble, 2000).

EPIDEMIOLOGY STUDIES OF NEW YORK TALC WORKERS:

Whatever the true nature of the talc, the correct classification ultimately rests on studies of exposed workers. To classify Vanderbilt talc as a carcinogen it must be shown that worker exposure to Vanderbilt talc increases the risk of lung cancer. The weight of evidence should support a causal association (e.g. be consistent with causal criteria including biological gradient, temporal relationships, moderate to strong association). If there is an association it should not be due to chance, bias and confounding exposures.

I will briefly discuss the epidemiology evidence regarding risk of lung cancer among workers exposed to NY and Vanderbilt talc.

The talc that NTP identifies as containing asbestiform fibers is NY state talc. The most relevant studies identified by NTP are SMR and case-control studies of Vanderbilt talc workers. There are five cohort mortality studies of Vanderbilt workers and one lung cancer case control study. Two of these studies (Brown et al, 1990; Delzell et al, 1995) are not cited by NTP. Kleinfeld et al (1974) is an early PMR (proportionate mortality ratio) study of NY state miners and millers. The characteristics and some results from these studies are summarized in Table 1.

Table 1: Summary of 6 cohort studies and 1 case control study of Vanderbilt workers

Reference	Inclusion Criteria	Follow-up	Lung Cancer Obs: RR	Lung Cancer: > 20 yr. Latency ≤ 1 yr. tenure	>1 yr. Tenure
Kleinfeld et al (1974)	260 miners/millers >15 yrs 1940-1969	1940-1969	13/6.08= 2.14 (1.14-3.66) PMR	-----	-------
Brown (1980); Dement (1979)	Worked 1/1/47-12/31/59; N=398	1947-6/30/75	9/3.3 = 2.73 (1.25-5.18)	N=5 Not analyzed by tenure	
Stille & Tabershaw (1982)	1947-12/31/77; N = 655 (Stille);	1947-12/31/78	10/6.37 =1.57 (0.75-2.89)	Not stratified by latency	
Lamm et al (1988)	N= 705 (Lamm)		12/5 = 2.40 (1.24-4.19)	6/0.89 = 6.74 (2.47-14.7)	2/1.48 = 1.35 (0.16-4.88)
Brown et al (1990)	Worked 1947-12/31/77; N=710	1947-12/31/83	17/8.21 =2.07 (1.21-3.31)	8/2.20 = 3.64 (1.54-7.04)	5/2.79 = 1.79 (0.58-4.16)
Gamble(1993): case control	N=22 cases		22cases/66 controls	10/23 = 1.00	8/30 = 0.61 (0.21-1.80)
Delzell et al (1995)	White males 1948-1989; N = 818	1948-1989	31/12 = 2.54 (1.73-3.61)	Latency not considered 17/4.8 =3.52 (2.05-5.64)	14/7.4 = 1.90 1.04-3.19)

Kleinfeld et al (1974) is a proportional mortality study of 260 miners with 15 or more years exposure. There were 108 total deaths, with 13 lung and pleural cancer observed deaths. There is confusion about the actual PMR for lung and pleural cancer. Kleinfeld et al (1974) indicated 12% observed and 3.7% expected, "approximately 4 times that expected." The ratio of these numbers is 3.24, which IARC (1987) more

correctly characterizes as a "three-fold overall increase" with one "peritoneal mesothelioma." Recalculating from Table 2 of Kleinfeld et al (1974) yields 13 observed cases and 4.48 expected cases, for a PMR of 2.91 (Table 2).

Table 2. Recalculation of PMRs for Carcinomas of the Respiratory Tract stratified by age from Table 2 of Kleinfeld et al (1974)

Age Group	Total Deaths	Observed: % obs	Expected* : % exp	PMR (95% CI)*
< 40	3	0 : 0%	0.05: 1.6%	0
40-59	47	4: 8.5%	2.44: 5.7%	1.64 (0.45-4.20)
60-79	54	9: 16.6%	1.94: 3.6%	4.64 (2.12-8.81)
80-84	4	0: 0%	0.044: 1.1%	0
Total	108	13: 12%	4.47: 4.83%	2.91 (1.55-4.97)

* = Calculated values.

Calculation of the PMRs from Table 4 of Kleinfeld (1974) yields 13 observed cases and 6.08 expected, for a PMR of 2.14. These expected proportions of respiratory cancer increased monotonically from 2% in 1940-4 to 7.7% in 1965-9. The expected numbers are based on the median of each of the 5-year periods rather than the 1955 rates in Table 2. The PMRs using expected numbers from the midpoint of the 5-year intervals are the most precise, so the most valid PMR for these workers with 15 or more years exposure is 2.14 (1.14-3.66). (See Table 3 for calculations.)

Table 3. Recalculations of PMRs for cancers of the lung and pleura stratified by calendar time from Table 4 of Kleinfeld et al (1974).

Calendar time	Total Deaths *	Observed: % obs	Expected*: % exp	PMR (95% CI)*
1940-44	7	0: 0%	0.14: 2.0%	0
1945-49	17	2: 11.7%	0.53: 3.1%	3.77 (0.46-13.6)
1950-54	8	1: 12.5%	0.34: 4.3%	2.94 (0.07-16.4)
1955-59	25	5: 20.0%	1.42: 5.7%	3.52 (1.14-8.30)
1960-64	28	3: 10.7%	1.88: 6.7%	1.60 (0.33-4.66)
1965-69	23	2: 8.7%	1.77: 7.7%	1.13 0.14-4.10)
Total	108	13: 12.0%	6.08: 5.6%	2.14 (1.14-3.66)

* = Calculated values.

IARC (1987) noted that no data were available on smoking or on cumulative exposure. Kleinfeld et al (1974) also comment that without smoking data it is not possible to account for the role of smoking "in accounting for the differences in the occurrences of malignancies" with asbestos insulators and anthophyllite asbestos miners.

Vanderbilt Talc Studies.

The remainder of the studies are of Vanderbilt workers. A few of the workers from Kleinfeld et al, (1974) are included in these cohorts.

Dement et al (1979) and Brown et al, (1980) are the same study, with analysis only by latency. Stille and Tabershaw (1982) and Lamm et al (1988) are the same cohort of Vanderbilt workers. Lamm et al (1988) got information on missing dates of birth to increase cohort size from 655 to 705 white males. Both studies analyzed only by $\pm$ 1-year tenure, but Lamm re-analyzed by latency and tenure for the OSHA hearings. Brown

et al (1990) is the same cohort as Lamm et al (1988) but with an additional 5 years of follow-up with analysis by both latency and tenure. Gamble (1993) is a case control study nested in the cohort of Brown et al (1990) with consideration of other occupational exposures and smoking. Delzell et al (1995) is the same cohort as Lamm et al (1988) but employees hired through 1989, adding 108 more men to the cohort with follow-up through 1989.

The most relevant studies of Vanderbilt workers are Gamble (1993) because of adjustments for latency, smoking and other exposures, and Delzell et al (1995) because of largest number of cases and quantitative estimates of exposure. These are the most important studies and should form the epidemiological basis for a carcinogenic classification of Vanderbilt talc. The reasons for this conclusion are as follows:

* The references to Brown et al (1979) and Dement et al (1980) are the same study published in two different places. This first NIOSH study has no analysis by exposure or tenure, no adjustments for potential confounding from other exposures and smoking, and the number of lung cancer cases is very small (n=9).

* The studies by Stille and Tabershaw (1982) and Lamm et al (1988) are of a larger cohort of Vanderbilt workers at the same plant. The study of Stille and Tabershaw (1982) is subject to selection bias. Lamm et al (1988) analyze by tenure but not latency with some consideration of other exposures. An unpublished version includes an analysis by latency and tenure. The number of lung cancer cases is increased but still small.

* Brown et al (1990) added 5 more years follow-up to the cohort of Lamm et al (1988), analyzed by both latency and tenure, and had 17 lung cancer cases. There is no adjustment for potential confounders. This study was not cited by NTP, but should supersede the previous cohort analyses of Vanderbilt workers. .

* Gamble (1993) is a case control study nested within Brown et al (1990). The number of lung cancer cases was increased to 22, and there was adjustment for potential confounding exposures for smoking, other talc exposures, and occupational exposure to carcinogens. Analysis was by latency and tenure and by smoking status.

. * Delzell et al (1995) increased the size of the cohort to 818 white men, 31 lung cancer deaths, and added individual-level estimates of dust exposure for a latency by exposure-response analysis. This study should supersede all the other cohort studies. It is the largest study of Vanderbilt workers with longest follow-up, analyses by latency and exposure with exposure variables of both tenure and cumulative dust exposure (in mg/m3-years).

EVALUATING WHETHER THERE IS A CAUSE-EFFECT ASSOCIATION.

IARC has suggested three criteria useful for assessing causality. To determine whether there is a causal association it "is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies." (IARC, 1997) These criteria will be discussed with regard to individual studies.

Then criteria of temporality, biological gradient, and strength of association that are useful for assessing causality will be discussed.

Following the discussion of causal criteria I will return to the question of whether confounding is a reasonable explanation for the elevated risks of lung cancer.

STUDY CRITERIA: What are the Primary Human Studies to Determine Whether Asbestiform Talc is Carcinogenic? The criteria that must be taken into account in evaluating both individual studies and the weight of evidence with regard to the causal criteria of strength of association and biological gradient are bias, confounding and chance.

* The presence of identifiable or apparent bias may lead erroneously to an association that in fact does not exist. Selection bias is possible in Stille and Tabershaw (1982) due to exclusion of 12.5% of the cohort because of missing data. Causes of death are not independent in a proportional mortality (PMR) study, as a deficit (or excess) in one cause will result in an excess (or deficit) in another. Kleinfeld (1974) is the only PMR study of NY talc workers under consideration.

* The presence of substantial confounding may also produce an erroneous association. Several potential confounding exposures have been suggested to explain the elevated risk of lung cancer in the cohort studies. These potential confounders include smoking, other talc exposures and other occupational exposures (and are discussed further below). Lamm et al (1988) considered other talc exposures posed a significant risk, but the data were from personnel records and may be incomplete. They had no data on smoking or other occupational exposures. Gamble (1993) found that smoking was a significant confounder that appeared to explain the elevated risks of lung cancer in the cohort studies. Other occupational exposures (both talc and non-talc) did not increase the risk of lung cancer in the case control study, and so therefore are not considered to be confounders. Delzell et al (1995) conducted internal exposure-response analyzes which reduced potential confounding effects due to smoking. None of the other studies had data or analyzes to adjust for confounding.

* Could the results be due to chance? All studies considered statistical significance. None of the studies showed statistically significant excess risk of lung cancer among workers with 20 or more years latency and 1 or more years tenure. Thus among the high exposure (high risk) group the elevated risk ratios could be due to chance.

IARC considers lack of clarity in any of these aspects of a study to "decrease its credibility and the weight given to it in the final evaluation." The greatest clarity on these issues comes from the case-control study (Gamble, 1993) and the largest cohort study (Delzell et al, 1995). These are the studies that should be given greatest weight in assessing whether the weight of evidence is consistent with a causal association.

CAUSAL CRITERIA: The question being addressed in this section is under "what circumstances can we pass from this observed association to a verdict of causation?" (Hill, 1965) Temporality can exclude a causal association if the putative cause does not come before the effect. Otherwise, none of the causal criteria "can bring indisputable evidence for or against the cause-and-effect hypothesis." (Hill, 1965). Further discussion of the causal criteria are found in Hill (1965), 1964 Surgeon General Report on Cancer

and Smoking, Rothman and Greenland (1998), Susser (1973) and IARC among many others. The more of these criteria that are satisfied the greater the weight of evidenced that observed associations are likely to be causal.

The causal criteria of temporality, biological gradient (or exposure-response trends), and strength of association are discussed. The causal criteria of consistency and biological plausibility will not be discussed. Since only Vanderbilt talc is described as containing asbestiform fibers, there is essentially only one cohort of exposed workers (albeit several studies). Although it is important, biological plausibility will not be discussed in this submission. Plausibility refers to the biological plausibility of the hypothesis, which is often based on the experimental animal data and *in vitro* experiments, and is a major part of the NTP documentation. For the weight of evidence to support plausibility, two requirements must be satisfied. One, a clear case must be made that Vanderbilt is morphologically like the asbestos in the studies used to support plausibility. That has not yet been done. Second, all the *in vitro* and *in vivo* studies of Vanderbilt talc must be included as part of the evidence. This also has not been done. Until this evidence is included in the case being made, there is no scientific justification for concluding that the criterion of biological plausibility has been satisfied.

As shown below, the weight of the evidence does not support the causal criteria, so the epidemiology studies DETRACT from the hypothesis that Vanderbilt talc is carcinogenic.

+ Temporality criterion. The exposure must precede the effect. For lung cancer the exposure should precede the diagnosis of lung cancer by 20 or more years (Brown and Dement, 1982). If the latency is less than 20 years or so, then it is unlikely that the exposure caused the disease. By this criterion there are 6 lung cancer cases in Brown et al (1980), 13 in Brown et al (1990), 18 in Gamble et al (1993) and 26 in Delzell et al (1995) where the lung cancer might be caused by Vanderbilt talc exposure.

Table 4. Lung cancer cases with 20 or more years of latency.

	Kleinfeld et al (1974) > 15 yr	Brown et al (1980)	Brown et al (1990)	Gamble (1993)	Delzell et al (1995)
Cases > 20 yrs latency	13/6.08 = 2.14 (1.14-3.66)	6 /1.3 =4.62 (1.69-10.1)	13/2.83= 2.60 (1.37-4.4)	18 smokers + exsmokers	26/8.4 = 3.09 (2.02-4.54)

The temporality criterion is discussed below with regard to whether the time since starting smoking or the time since talc exposure began is more coherent with our knowledge of the natural history of lung cancer.

+ Biological Gradient criterion. A strong indication of causality is when the risk of disease increases with the amount of exposure. Tenure and cumulative exposure to dust (mg/m3-years) are the measures of exposure. A strong indicator of causality occurs if the risk of lung cancer increases as tenure/cumulative dust increases. **The lack of biological gradients in the studies of talc workers detracts from the hypothesis that Vanderbilt talc is carcinogenic.**

Table 5. Exposure-response relationships for lung cancer (20 or more years latency except for cumulative exposure (Delzell et al, 1995)

	Lamm and Starr	Brown et al (1990)	Gamble (1993)	Delzell et al (1995)
> 20 years latency	(8) 3.38 (1.45-6.65)	(13) 2.60 (1.37-4.41)	Smokers + exsmokers	(26) 3.09 (2.02-4.54)

> 1 year tenure < 1 year tenure	(2) 1.35 (0.16-4.88) (6) 6.74 (2.47-14.7)	(5) 1.79 (0.58-4.16) (8) 3.64 (1.54-7.04)	8/21 0.65 (0.21-2.0) 10/17 1.0	
15-36 yrs tenure 5-15 yrs tenure < 5 yrs tenure			5/10 1.00(0.28-3.59) 0.50(0.05-4.98) 12/24 1.0	(7) 2.15 (0.86-4.42) (19) 3.71 (2.23-5.8)
1705+ mg/m3-yrs 326-1704 63-325 0-62 mg/m3-yrs				(7) 0.45(0.17-1.2) (6) 0.68 (0.24-1.9) (6) 0.74 (0.27-2.1) (10) 1.0

All of the studies showed that more than a majority of the lung cancer cases had short (< 1 year) employment histories, and the short-term workers had higher risks than the longer-term workers. The risk of lung cancer among longer- term workers was not statistically significant, although the number of cases was small. The case control study showed an inverse relationship with tenure in an internal comparison comparing smokers + exsmokers with smoker + ex-smoker controls. Delzell et al (1994) showed an inverse relationship with dust exposure in an internal comparison (with 3 cases having < 20 years latency). These studies suggest there is an inverse biological gradient, a strong indication against causality.

Delzell et al (1995) also assessed risk of lung cancer by work area. Mill workers and mine workers had similar cumulative dust exposure, but the excess risk was concentrated in the miners with an SMR of 4.73 (2.80-7.47) and unexposed workers with an SMR of 4.33 (0.87-12.64). Mill workers had an elevated SMR of 1.50 (0.60-3.09 that is consistent with random variability.

These comparisons by work area and the inverse relationships with exposure indicate Vanderbilt dust *per se* is not producing the excess risk of lung cancer, and is strong evidence against the hypothesis that Vanderbilt talc is a carcinogen.

Brown et al (1980) suggest that increasing risk with increasing latency is consistent with an occupational etiology. However, an analysis by latency alone includes workers that do not meet the temporality criterion and there is coincident latency from smoking. The question of smoking is discussed further below. The consistent lack of exposure-response trends clearly provides more clarity and weight than the analysis by latency alone. The internal exposure-response analyses also tend to reduce the potential for confounding because the comparison is between workers from the same cohort.

+ Strength of Association criterion. A large relative risk is more likely to indicate causality than a weak association is. A weak association is more susceptible to bias and confounding in producing an erroneous association. A weak association is generally considered to be less than about 2-fold.

The most appropriate category to assess strength of association is in the high exposure group with 20 or more years latency. In Brown et al (1990) the SMR is 1.82 (0.21-6.36) for lung cancer cases with 20-36 years tenure, and 1.79 (0.58-4.16) for cases with more than one year of tenure. The corresponding ORs is 1.00 (0.28-3.59) for smokers + exsmokers with 15-36 years tenure and 0.65 (0.21-2.0) for cases with 1 or more years tenure. Delzell et al (1995) in the group with 5 or more years tenure had a nonsignificant elevated SMR of 2.15 (0.86-4.42). The risk ratio in the cases with highest cumulative exposure was less than one, 0.45 (0.17-1.2) compared to cases with minimal cumulative dust exposure.

The strength of association in the highest exposed groups is generally weak in external comparisons and nonexistent in internal comparisons. The increased risk ratios could be due to random variability. These findings do not support the hypothesis that Vanderbilt talc is a carcinogen.

MORE ON QUESTION OF CONFOUNDING

Now that the relevant studies have been reviewed to assess temporality, biological gradient and strength of association, the important question of confounding will be addressed more directly.

The evidence is supportive that the increased risk of lung cancer in these studies can be explained in part or wholly as due to confounding from smoking. Other hypothetical risk factors do not appear to be important confounders.

Brown et al (1990) comment that the high risks of lung cancer are in part due to exposure to Vanderbilt talc, although cigarette smoking and other occupational exposures may also have contributed. They speculate that the high lung cancer mortality among short-term workers might be explained by:

1) Employment in other NY talc mines;

2) Exposure to lung carcinogens from employment prior to Vanderbilt and including other NY talc mines and mills;

3) Very high exposures in their short employment at Vanderbilt, especially in the early years of the mining operation;

4) Cigarette smoking.

Each of these issues were addressed in the case control study (Gamble, 1993).

1) Potential Confounding from Non-talc employment: A complete work history was obtained for each case and control. Non-talc jobs were ranked as "probable,' 'possible,' and 'none' for risk of lung cancer. **There was no trend for risk of lung cancer to increase with non-talc exposure**, so there was no apparent confounding from this variable and no adjustment for this variable was made in the analyses.

Table 6: Analysis of potential confounding from non-talc employment (Gamble, 1993)

Score: (panel score X years worked)	Cases	Controls	Odds Ratios (95% confidence intervals)
221-533	3	13	0.55 (0.12-2.46)
121-220	6	13	1.10 (0.31-3.91)
51-120	5	21	0.56 (0.16-2.03)
0-50 (Referent)	8	19	1.00

2) Potential Confounding from Other Talc (non-Vanderbilt) exposure: Non-Vanderbilt talc employment added little to Vanderbilt employment for either cases or controls: 1.1 year to 6.6 years for cases and 0.7 years to 9.2 years for controls. **There was no significant trend for the risk of lung cancer to increase as years of total talc employment increased among smokers + exsmokers with 20 or more years latency.**

However, smokers + exsmokers with more than 15 years total talc exposure had a nonsignificant elevated OR.

Table 7: Analysis of potential confounding from other talc exposures (Gamble, 1993)

Total Talc years: > 20 yrs latency	Cases: Smokers + Exsm	Control: Smoker + Exsm	Odds Ratios (95% CI)
15-41 years tenure	6	10	1.42 (0.41-4.87)
5-15 years tenure	1	4	0.59 (0.06-5.90)
<5 years tenure	11	26	1.0

Exposure at non-Vanderbilt mines appears to be considerably higher than in the Vanderbilt mine and mill. Dement and Zumwalde (1979) reported dust counts collected at Vanderbilt in the mid-1970s while Kleinfeld et al (1967) summarized dust counts in surrounding mines and mills from before 1945 to the 1970s. Mill concentrations in surrounding mills were 10-300 times higher than in the Vanderbilt mill, while mine concentrations were roughly similar except prior to 1945. Six (27%) of the cases had worked at surrounding mines and mills, mostly in the 1940s. Fourteen (21%) of the controls had worked in surrounding facilities in approximately the same time period, although three had worked in the late 1930s.

Concentrations in mppcf: range	Dement and Zumwalde (1979)	Kleinfeld et al (1974) Mines and Mills in Upper NY State around the Vanderbilt mine and mill		
	Late 1970s	1972(range of avg)	1946-65	Pre-1945
Mine	1.5-15.8 (1.0)	3-7 mppcf (0.6)	9-19 mppcf (1.6)	120-818 (54)
Mill	0.5-3.6 (1.0)	7-36 mppcf (10)	28-43 mppcf (17)	69-1227 (324)

The lack of a gradient with total talc tenure among smokers + exsmokers detracts from the hypothesis that talc exposure is associated with increasing risk of lung cancer.

3.) Very High Exposures for Short-term workers in Early Years of Work.

Gamble (1993) matched controls on date of hire. The match was quite good, as mean date of hire for both cases and controls was 1949. **Matching on date of hire indirectly accounts for intensity of exposure and increases the likelihood of similar exposures for cases and controls.** There is no evidence that cases were preferentially placed in very high exposure jobs; when workers were hired there was no way to predict who would be cases or controls, long-term or short-term workers. Assuming workers were hired more or less at random, then cases and controls have equal opportunity to be assigned high and low exposure jobs. **Thus there is evidence against the hypothetical explanation of high risk among short-term workers because of very high intense exposures.**

4) Confounding by Smoking.

The NIOSH investigators (Brown et al, 1980, 1990) have suggested smoking is an unlikely explanation for the elevated lung cancer risks. To address this question in the cohort studies one must determine what increased risk has to be explained. The overall SMR of 2.73 (1.25-5.18) in the first NIOSH study was said by Brown et al, (1980) to be

too high to be explained by smoking. In a heavy smoking population they estimate "smoking alone would increase the expected lung cancer mortality risk by no more than 49 percent," (a risk ratio of 1.49). Thus Brown et al (1980) suggest cigarette smoking *per se* is unlikely to account for the 2.73-fold increased risk of lung cancer among the 9 talc miners and millers." However, the actual SMR lies somewhere between 1.25 and 5.18. And when the actual smoking patterns of the cases and controls are used in an Axelson-type adjustment, smoking alone can explain about a two-fold risk. Since the hypothetical figure of 1.49 is above the lower confidence of 1.25, the idea that smoking could be a cause of the elevated risk cannot be excluded.

In the second NIOSH study the overall risk ratio for lung cancer was 2.07 (1.21-3.31) (Brown et al, 1990). Using an Axelson (1978) adjustment, Brown et al (1990) estimate that "even if 100% of the cohort were smokers, the risk for lung cancer would have been increased only by 60% or an SMR of 160." The actual value of the SMR lies somewhere between 1.21 and 3.31. The lower 95% confidence interval of the risk ratio falls well below the 1.60 suggested by Brown et al (1990). Thus smoking can explain at least some of the increased risks using the estimates proposed by the NIOSH authors.

Note that 91% of the cases were smokers and 9% were ex-smokers compared to 64% and 9% respectively for the controls (Gamble, 1993).

The risks associated with smoking are greater than the lower 95% confidence intervals of the overall risks of lung cancer. Therefore, smoking is a viable cause of at least some of the overall excess in the NIOSH studies, and random variability is also a possible explanation (Brown et al, 1980, 1990).

But these are not the most relevant risks that need to be explained, since some of the lung cancer cases have less than 20 years since first exposure to talc. Four of the lung cancer cases with less than 20 years talc latency have an average of 32 years latency (25-35 years) latency since starting smoking (from Gamble, 1993). For these cases, smoking is a more likely explanation than talc.

The more appropriate risk that needs to be explained is among the most exposed cases with 20 or more years latency. The SMR in the group with greater than 1 year tenure is 1.79 (0.58-4.16) (Brown et al, 1990). This risk could be due to random variability. An Axelson-type adjustment suggests the risks associated with smoking could be 1.29 (0.42-2.99) using actual smoking data. The SMR is 2.15 (0.86-4.42) in the high exposure category of Delzell et al, (1995) with about 1.55 (0.62-3.18) explainable by smoking. Random variation is a probable cause of the elevation.

Elevations in lung cancer risk among high exposure groups could be chance findings as they are not statistically significant. If there is a true risk, potentially all or a substantial portion of what might be an increased risk can be explained by smoking. These indirect adjustments for smoking suggest that smoking, as a causal agent cannot be excluded.

Gamble (1993) conducted a direct test of the smoking hypothesis. The smoking status of all cases and controls was determined. Since all cases were smokers or exsmokers, a comparison between cases and controls who were smokers and exsmokers was conducted. The odds of longer tenure were no greater among the cases than among the controls, a finding consistent with a smoking rather than an effect of exposure.

Another way to examine the role of smoking and exposure is to evaluate their respective latencies. The mean time from date of hire till death for chrysotile asbestos

miners and millers was about 40 years, regardless of smoking habits (Liddell, 1980). The mean years latency among asbestos workers with very high exposure and high risk of lung cancer is about 28-34 years (Selikoff et al, 1980; Knox et al, 1968; Dement et al, 1983). It is unlikely that asbestos workers exposed to true asbestos at high concentrations would have a longer latency than workers exposed to lower exposures of talc (with or without asbestiform fibers).

Mean time from beginning smoking till death from lung cancer was 40 years. Smokers have a latency of about 40 years (Liddell, 1980; Wynder and Stellman, 1977). Therefore, the criterion of temporality suggests smoking is a more plausible risk factor for lung cancer than exposure to talc for these workers.

Coincident Latencies: Temporal relationships are more suggestive of a smoking etiology than talc or asbestos etiology.

SUMMARY

The appropriate studies to assess risk of lung cancer among workers exposed to Vanderbilt talc is the last update of the Vanderbilt cohort which adds an exposure-response analysis with cumulative exposure (Delzell et al, 1996) and the lung cancer case control study nested within this cohort (Gamble, 1993) which adjusts for confounding. These studies have longer follow-up, more lung cancer cases, and an analysis by latency and tenure and cumulative exposure such that in the aggregate neither bias nor confounding compromise the validity of the studies. When elevated risks occur in high risk groups they may be the result of random variability.

These studies show that the only significant excess risk is among short-term workers and that there is an inverse exposure-response gradient using both external controls (e.g., Brown et al, 1990; Delzell et al, 1995) and internal controls (Gamble, 1993; Delzell et al, 1995). The associations are weak and not statistically significant, and smoking is a plausible explanation for the increased risk in the workers with longer exposure and adequate latency. Talc, as an etiological agent, is not coherent with the lung cancer latency shown in highly exposed asbestos workers. Smoking as an etiological agent is coherent with latency shown for smokers.

In sum, the weight of the evidence from these studies does not satisfy the criteria for a causal relationship between Vanderbilt talc exposure and risk of lung cancer. The associations are weak and elevated risks could be due to chance and confounding from smoking. There are consistent inverse exposure-response gradients where exposure variables are both tenure and cumulative talc dust. The temporality criterion is more consistent for a smoking etiology than for a talc etiology.

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November 28, 2000

Dear Dr Wolfe,

As promised in my recent letter, I attach my submission on talc for consideration by NTP. I look forward to hearing from you concerning the scheduling of my short oral presentation to address the salient points in my submission.

Yours Sincerely,

Graham W Gibbs
MSc PhD ~~LRSC~~ ROH.

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AN EVALUATION OF THE EPIDEMIOLOGICAL EVIDENCE CONCERNING "TALC" AND RESPIRATORY CANCER IN HUMANS WITH SPECIFIC ATTENTION TO "TALC" AS PRODUCED BY THE GOUVERNEUR TALC COMPANY [A SUBSIDIARY OF THE R.T. VANDERBILT COMPANY INC] AT ITS MINES IN NEW YORK STATE.

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November 27, 2000

AN EVALUATION OF THE EPIDEMIOLOGICAL EVIDENCE CONCERNING "TALC" AND MALIGNANCY IN HUMANS WITH SPECIFIC ATTENTION TO "TALC" AS PRODUCED BY THE GOUVERNEUR TALC COMPANY [A SUBSIDIARY OF THE R.T. VANDERBILT COMPANY INC] AT ITS MINES IN NEW YORK STATE.

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QUALIFICATIONS AND EXPERIENCE.

I received a Baccalaureate [BSc] degree in Geology and Chemistry at the University of London, England in 1966, a Master of Science [MSc] degree in Geological Sciences [Dean's Honours List] at McGill University in 1969 and a Doctor of Philosophy degree [PhD] in Epidemiology [Dean's honours List] at McGill University, Montreal, Canada in 1972. I am a Licentiate of the Royal Society of Chemistry [LRSC] and a Registered Occupational Hygienist [ROH] through the Canadian Registration Board of Occupational Hygienists. I have worked in the occupational and environmental health fields for more than 40 years. My curriculum vitae and list of publications are attached [APPENDIX A].

BACKGROUND.

The R.T. Vanderbilt Company Inc., through the Environmental Sciences Laboratory, Brooklyn College of the City University of New York, have requested that I undertake a review of the various epidemiological studies of workers employed by the Gouverneur Talc Company in New York State to determine if they support or otherwise the designation of talc from this deposit as a carcinogen. The following is my report on this matter.

DEFINITIONS

The "Draft Background Document" for "Talc Asbestiform and Non-Asbestiform" is not clear in its definition of "Talc Asbestiform". The summary statement on page iii and v refer to: "Talc containing asbestiform fibers". Does this mean talc containing asbestos fibres or talc containing non-asbestos asbestiform fibres, both or talc containing elongated particles with aspect ratios exceeding 3:1, but with diameters less than about 3-4 micrometres? On page 5, the document notes "Natural talc deposits and commercial talc products are found to contain serpentines (chrysotile, antigorite and lizardite) and fibrous and non-fibrous amphiboles [Rohl et al 1976]. This form is also known as asbestiform talc, talc [containing asbestos] or talc containing asbestiform fibres."

If this is the definition being adopted by NTP, and if the term fibrous amphiboles in this definition refers to amphibole asbestos, then, it is not clear why a separate nomination would be needed for talcs containing asbestos as the asbestos minerals have already been classified as carcinogenic. The presence of asbestos fibres in a talc does not render the mineral talc carcinogenic, but the mixture, dependant on the asbestos fibre type, fibre dimensions and percentage may increase cancer risk.

On the other hand, the "Draft Background Document" cites studies of GTC miners and millers in support of the nomination. Because of this, it must be assumed the author of the "Draft Background Document", RG1 and RG2 consider that these workers are exposed to "talc asbestiform". This presents a definition problem because there is expert mineralogical opinion that GTC workers are not exposed to asbestos although they may be exposed to cleavage fragments meeting the OSHA definition of a fiber, talc fibers and transitional fibers. I will leave this technical issue to those who have studied the ore, product and airborne dusts and in this submission, the term "GTC talc" will refer to the mixture of minerals produced as "talc" by the Gouverneur Talc Company from its New York Deposit and include all its components. When the unqualified term "talc" is used, it refers to the minerals and mineral habits present in a particular talc.

CRITERIA TO DECIDE WHETHER GTC TALC IS CARCINOGENIC

According to the background document, listing a substance as a "known human carcinogen" requires that there is sufficient evidence from studies in humans, "which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer". The criteria for listing a substance as "Reasonably anticipated to be a human carcinogen" is "There is limited evidence of carcinogenicity from studies in humans, which indicates causal interpretation is credible but that alternative explanations such as chance, bias or confounding factors could not adequately be excluded" or there is sufficient evidence of carcinogenicity from studies in experimental animals.

The report of the Carcinogens review group RG1 concluded that talc containing asbestiform fibers is known to be a human carcinogen and RG2 concluded that talc containing asbestiform fibers is reasonably anticipated to be a human carcinogen. Both conclusions are based largely on studies of talc miners and millers and "asbestos" exposure is mentioned.

In order to correctly interpret the results of the GTC worker studies, it is important that any pre-conceived notion that asbestos may be present and must be responsible for any increased respiratory cancer risks be set aside. The evidence for or against classifying talc as produced by GTC as a carcinogen should rest on the evidence from the studies of talc workers and determine if the exposures are causally associated with increased risks of respiratory cancer or that a causal interpretation is credible. The experimental data are part of this evaluation. Experimental data will not be discussed in this report, but must be considered in relation to plausibility. Some of the criteria which are often used in deciding on causality in epidemiological studies are listed in APPENDIX B.

LUNG CANCER RISKS IN GTC WORKERS.

The first study to include some GTC workers was a proportional mortality ratio [PMR] study of miners and millers in New York State who had had 15 or more years of exposure to talc dust in 1940 or between 1940 and 1965 [Kleinfeld et al 1997]. Follow-up began in 1940 which was, seven years before GTC began production. It is evident that the number of GTC workers included in this cohort would have been very limited. The study indicated a high PMR from lung cancer, but this needs to be interpreted with considerable caution as 30% of deaths in the cohort were due to pneumoconiosis or complications, a cause of death not common in the referent US general population. It was also based on the US proportional mortality for only one year. The role of smoking was not assessed and the characterization of the dusts to which the workers were exposed was general with no reference to mineral habit. All cases of lung cancer had initial exposure before 1945 when wet drilling was introduced, but "there was no evidence to indicate that there was a direct relationship between duration of exposure prior to the onset of wet drilling and the occurrence of pulmonary carcinoma". In retrospect, this is perhaps the first indication that the lung cancer risk may not be exposure related.

Brown et al [1980] reported on the NIOSH study. This study has been well critiqued [eg: Gamble 1985] and there is little value in revisiting this cohort of 398 workers as the study has now been updated and superseded by more recent information. For the record, the study did not examine exposure-response or take smoking into consideration.

Stille & Tabershaw [1982] studied 744 men employed January 1 1948 through December 31 1977. After exclusions for lack of information, 655 white male talc workers were available for analysis. The mortality from lung cancer compared to US white males was not statistically significantly increased [SMR = 157 Observed = 10] in men who worked at the plant [assumed to be GTC] but was statistically significantly greater [SMR=214 observed 8] in men who worked elsewhere before joining the plant. Incidentally, most of the criticisms levelled at this report by IARC and noted the "Background Document, page 20", also apply to the original NIOSH study in 1980 and Vermont study by Selevan et al [1979] as none of these studies took account of smoking or involved an examination of exposure-response.

Lamm et al [1988] reported on what appears to be essentially the same cohort as studied by Stille and Tabershaw [1982]. They found that 425 had worked for GTC for more than one year and 280 for less than one year. They categorized each job on the pre-employment history by likelihood of increasing lung cancer risk. The overall mortality from respiratory cancer was elevated [SMR = 240], but as reported by Stille & Tabershaw [1982], the lung cancer mortality was concentrated in men employed for 1 year or less [SMR=317] and concentrated in those who had worked in jobs carrying a lung cancer risk before joining GTC [SMR=316]. The respiratory cancer risk was lower in persons with longer duration of employment. Importantly they noted that there were no differences in the initial jobs assignments at GTC for workers who left within 1 year and those who stayed. This observation does not support the hypothesis put forward by Brown et al [1980] that the excess lung cancer risk is due to short high exposures encountered by short-term workers. This study did not have smoking information available.

In 1990, Brown et al [1990] expanded the original NIOSH cohort definition, increasing the cohort size to 710 white males employed at any time between 1947 and 1978, and updated the

vital status to December 1983. The overall SMR for lung cancer was still elevated [SMR 207] compared to the experience of US males. However, the authors found that the SMR for workers with 20 or more years of latency and less than 1 year tenure was 357 [CI: 154, 704], while those workers with more than 20 years of latency and more than 1 year of tenure had an SMR = 178 which was not statistically significant; ie could have occurred by chance. Again, detailed smoking histories were not available. This difference in risk between the short term and long term employees would not be the pattern anticipated if the lung cancer excess were related to the GTC exposures unless the short-term workers had higher talc exposures than longer term workers. The study by Lamm et al [1988] did not suggest that this was a likely scenario. Again an exposure response study was not undertaken. This report was not cited in the Background Document.

The reason for the excess lung cancer reported by Kleinfeld et al [1967] and Brown et al [1980] was not known in 1986 when IARC [1987] deliberated on talc. It was probably inferred because the studies involved talc miners and millers and minerals such as "tremolite and anthophyllite [asbestiform and nonasbestiform habits] were mentioned. In fact, there had been no exposure-response studies and smoking had not been taken into account. The results of the larger NIOSH study [Brown et al 1988] or the results of studies discussed in the following paragraphs were not available to them.

Four years after the IARC [1987] review of Talc, the interpretation of the data were still being debated [Morgan & Reger 1990]. However by that time, it was known that:

> There was an increased mortality from lung cancer in GTC cohort members. This was observed by all researchers, but this should not be surprising as they were studying the same or overlapping cohorts.
>
> The excess mortality from lung cancer was greater in the workers employed for less than 1 year than in those employed for more than 1 year.
>
> The excess did not seem to be due to different initial job assignments for workers with short and long term employment.
>
> The excess lung cancer mortality seemed to be explained in part by prior employment in other "cancer risk" industries.

Since 1990, two studies have become available which are extremely important in understanding the epidemiological studies and are the only ones available which provide information on which to determine whether or not the excess lung cancer in GTC workers is associated with exposure to GTC talc.

The first study is the nested case-control study reported by Gamble [1993]. The 22 cases selected for study were those dying with lung cancer in the NIOSH update cohort of 710 white males studied by Brown et al [1990]. There were 3 controls per case, matched as closely as possible for date of birth and date of hire. Controls had to survive the case. Work history information was obtained from GTC files and tobacco use and additional work history information was obtained from the cases and controls or from relatives and friends. Smoking status was obtained for all

cases and controls. A panel of epidemiologists and occupational hygienists classified the non-talc jobs held by the cases and controls as to the risk of lung cancer associated with them on a scale of probable [score 3], possible [score 1], or none [score 0]. The composite score was developed for each man by multiplying the score for each job by the time spent in that job and summing the results over all jobs. The total scores were broken into 4 categories and estimates of the odds ratios for each category were then used to determine if this index of work at other than GTC jobs increased the risk of lung cancer. The author analyzed the data with and without non-GTC talc experience and took latency into account. The important findings were as follows:

- In an analysis to determine lung cancer risk in relation to smoking, the odds ratio in smokers was 5.71 when the odds ratio for ex-smokers and no-smokers was set at 1.00. This risk was 6.55 in persons smoking more than >40 cigarette/day smokers. There were no no-smoking lung cancer cases. It is evident that smoking has the potential to play an important role in the lung cancer experience of these workers.

- All workers had had non-GTC jobs. However, there was no increasing trend in the odds ratios for the risk of lung cancer with the "non-talc employment" indices. This indicates that workers were not dying of lung cancer as a result of working elsewhere. It is unfortunate that the author did not also carry out this analysis with a 20 year latency, to determine whether the most relevant employment in non-GTC jobs was associated with an increased lung cancer risk as this was suggested by previous research. For this reason the possibility that work elsewhere contributed to the lung cancer risk cannot be totally excluded.

- When only smokers were analyzed, the case control studies showed that the odds ratios for lung cancer risk by tenure at GTC with and without a 20 year latency showed no increasing trend and odds ratios remained below 1.00 as tenure increased. In fact the results consistently suggest that the risk of lung cancer decreased significantly with tenure at the plant. This pattern did not change in any important way when non-GTC talc exposure were added. This is not consistent with exposures at the plant being responsible for the apparently increased risk of lung cancer in the cohort unless tenure does not reflect exposure.

- The decreasing pattern of risk with increasing tenure would occur if the risk of the short tenure workers was elevated [for whatever reason]. The fact that it was increased was suggested in previous studies. In this regard it is important to note that Gamble did analyze the data excluding men with less than 20 years latency and less than both 1 year of tenure and men with less than 3 months of tenure. In the latter case, 11 lung cancer cases were removed. The case-control analysis restricting the analysis to smokers and setting the odds ratio for the 3 months - 5 years of employment at 1.0 showed that workers employed 15-34 years with more than 20 years since first employment had an odds ratio of 0.73.

The use of tenure as a surrogate for exposure has limitations. First, if there are non-exposed workers, tenure assumes exposure. Second, if there are large variations of exposure over time, tenure would not reflect these and this could affect the tenure-response relationship observed. Further the numbers become small [9 cases] when the short term workers are excluded. In spite

of these limitations, the absence of an increasing trend of lung cancer risk with increasing tenure after a latency of 20 years and after eliminating short term workers is not supportive of a GTC employment etiology.

The question now remains as to whether the dust exposure of workers in the GTC mine and/or mill are associated in any way for the increased risk of lung cancer. The second study attempts to answer this question [Delzell et al 1995]. It is unfortunate that this study has not been published. However, it was reviewed by 4 reviewers and their collective comments are available [Boehleke 1994].

In this study, individual cumulative respirable dust exposures were estimated for all GTC cohort members. These estimates were based on a job-exposure matrix. This consisted of an average respirable dust concentration in each work area and calendar year for the period 1948 through 1989. Historical dust concentrations exposures in various work areas by time periods were rated by a knowledgable panel of GTC employees. Special dust sampling surveys were conducted and paired respirable dust and dust count samples collected and used to convert historical dust count data to gravimetric respirable dust concentrations.

Baseline dust concentrations were based on the results of the special survey and a NIOSH survey. Past dust concentrations were then estimated by weighting baseline concentrations by the scores developed for the various time periods. These estimated past concentrations were then validated against historical dust measurements. It appears that a carefully considered approach was used to obtain respirable GTC talc exposure estimates which could be used to develop individual exposures for use in evaluating exposure-response.

The cohort consisted of 818 white men who worked for at least 1 day at the GTC from 1948 through 1989 and who had known birth and employment dates. The follow-up period was January 1 1948 through December 31 1989. There were 46 men with no work history who had a median duration of employment of 0.19 year. Their exclusion would not impact the risks of longer term workers. Twenty eight percent of the cohort were deceased. Causes of death were available for 222 [98%] of the 225 deaths. It should be noted that 344 [42%] of workers worked for <1yr and 521 for <5 years.

Compared to US white men, the cohort had an SMR from all causes of 141 [95% CI=123-161]. Excess mortality was observed for several causes of death including circulatory diseases, non-malignant respiratory diseases and cancer [SMR = 154, 115-200, observed = 54]. The cancer excess was mainly due to lung cancer [SMR 254, 173-361 observed = 31]. This finding of an overall excess of lung cancer is similar to that of earlier investigators. The use of local rates did not change the results.

For lung cancer, 22 of the 31 deaths occurred in men with less than 5 years of employment. The SMR did not rise with increasing length of employment within any category of years since hire. However, a statistically significant excess was present for the group of workers with less than 5 yrs of employment and more than 20 years since hire. For workers with more than 5 years of employment with 20+ years since hire there was a non statistically significant increased risk of lung cancer [SMR = 215, 86-442, observed = 7]. Thus, in the 20+ years since hire workers, the SMR of those employed for a short period exceeded that of the longer term workers. This argues

against a GTC work related factor being responsible for the observed increased risk of lung cancer.

The overall excess of lung cancer was concentrated in men employed in the underground mine [SMR = 440, 262-695, Observed = 18]. In fact the excess lung cancer mortality was in men who were only employed in the mine [SMR = 473, 280-747, Observed =18].

In contrast, there was only a small non-significant increase in lung cancer mortality in mill workers [SMR = 139, 56-287, observed = 7], a group with similar exposures to the underground workers. Such an increased risk might be explained by smoking [but this cannot be determined as smoking data were not available]. NMRD was in excess in millers [SMR = 321] and in underground miners [SMR = 349]. If talc were responsible for the excess lung cancer, one would have expected the same pattern of mortality of lung cancer mortality in both the millers as well as miners.

Lung cancer mortality was also increased among men who were exclusively employed in unexposed jobs [SMR= 443, 87-1264, Observed = 3]. This again, on small numbers, argues against a GTC talc etiology for the lung cancer excess.

When exposure-response was examined, there was an inverse relationship between lung cancer mortality and estimated cumulative dust exposure. The relative risk [RR] was 0.66 [CI: 0.32-1.4] for men with cumulative exposures greater than or equal to the median exposure versus those below the median value. Analyses by quartiles also suggested an inverse association. When men with less than one year of GTC employment were excluded, the RR for the same comparison was 0.62 [CI: 0.22-1.8].

All 7 subjects who had reportedly died with pneumoconiosis or interstitial lung disease had cumulative exposures above the cohort's median value. This suggests that the cumulative index of exposure is relating sensibly to mortality from pneumoconiosis, but that there is no evidence that the cumulative exposure to GTC talc relates sensibly to the lung cancer risk observed in this industry.

Two deaths from mesothelioma were reported. The one mesothelioma case had only 15 years between hire and death. In the Quebec chrysotile miners and millers there was not a single case with less than 20 years from first exposure to death. The other mesothelioma case had worked for several years on the construction of another talc mine before his GTC employment. At GTC he worked as a draftsman during mill construction in 1948-49 and worked outdoors. After leaving GTC he worked in removing, installing and maintaining oil heating systems where the possibility of asbestos exposure cannot be excluded. Thus, neither case is likely linked to GTC employment.

In addition to examining the relationship between cumulative respirable dust exposure and lung cancer mortality [not done in any other study], this cohort was larger than the original and updated NIOSH studies; the follow-up period was longer by 7 years than the most recent NIOSH study; analyses were performed using national, regional and local rates; internal comparisons were done and a major effort was undertaken to ensure that the cohort was complete using IRS 941 records. Unfortunately, tobacco consumption was not taken into account and is a weakness in hat we do not know whether the persons with low cumulative exposures smoked more than those

with high cumulative exposures. I think this is unlikely, based on my experience with other industries, but we do not know.

While the authors note that the use of an inappropriate index of exposure is another potential weakness, it would reasonably be expected that a higher respirable dust exposure would mean a higher exposure to any pertinent carcinogenic constituent of the GTC talc if there were any, so while at most, reducing the slope of an exposure-response relationship, it would be highly unlikely to reverse it. It is unfortunate that Delzell et al did not gather smoking or non-GTC employment information and carry out a nested case-control study to determine if they offer a possible explanation for the decreasing risk of lung cancer with increasing cumulative GTC talc dust exposure.

INFORMATION FROM OTHER STUDIES

There are other studies, some of which were not evaluated by IARC which are pertinent to the issue of respiratory cancer risks associated with talc.

Rubino et al [1976] followed 1514 miners and 478 millers in Italy. They separated the miners and millers because they considered the mine air dust to include certain amounts of inhalable silica. The talc was reasonably well characterised with no amphibole or chrysotile asbestos detected "in any amount in rocks and in inclusions". Rubino et al examined the risk of lung cancer in relation to 3 categories of cumulative exposure levels and showed no increasing risk with either level of latency. They also did not find any increased risk in miners compared to millers. The study used an external comparison population in the area and also internal comparisons. IARC expressed concerns about their comparison group. In a later paper [Rubino et al 1979] expected deaths were recalculated using Italian white male rates, which would have eliminated this concern. There was still a deficit of lung cancer in the miners and millers and no increase in risk with increasing cumulative exposure to "talc". This study does not support an increased lung cancer risk associated with their talc which contained quartz, muscovite, chlorite, garnet, carbonates [calcite and magnesite]. Talc or other fibers were not mentioned as present or absent.

Wergeland et al [1990] conducted a small study of 94 talc miners and 295 talc millers in Norway. Their talc was described as "non-asbestiform" talc with low quartz content. However, the talc contained trace amounts of tremolite and anthophyllite. Fibres were reported to have been detected near the "detection limit for optical microscopy" and low fiber content confirmed by electron microscopy. It is not known whether these were asbestos fibers or talc fibers. The main minerals in the talc deposit are talc and magnesite. In addition the ore contains magnetite, chromite, chlorite and antigorite with adjacent rocks containing serpentine, mica, feldspar, calcite and the amphiboles, hornblende and tremolite. Fibers, identified as tremolite, anthophyllite and talc were particles fulfilling the fiber definition of having a length: diameter ratio greater than 3:1. Smoking information was available. The numbers in the mine were too few to meaningfully interpret, but in the mill there was no excess incidence of lung cancer.

Selevan et al [1979] carried out a mortality study of what was described as "non-asbestiform" talc in Vermont. Quantitative estimates of "talc" exposure were not made, so the talc exposure-response relationships were not examined. It was of interest that there was a significant increase in respiratory cancer mortality in the miners but not in millers. It is perhaps relevant that if "talc"

were responsible for the increased risk of lung cancer, then one would have expected to see the excess in both the millers and miners.

COMMENT

There seems to be little doubt that the overall lung cancer risk in the various GTC cohorts is elevated. On the other hand, virtually all the epidemiological evidence points away from the lung cancer increase being related to the GTC talc exposure. The excess lung cancer in the GTC cohort is present in miners but not in millers. Tenure and cumulative exposure, trend in a direction contrary to that expected if there were a link with GTC talc exposure. This trend holds when short term workers are excluded. One can only speculate on reasons for the high overall mortality and mortality from lung cancer. Smoking seems one likely candidate, but seems unlikely to explain some of the very high SMR's observed for underground miners. Miners encounter minerals which may entail exposures which are diluted with other dusts in the mill, so the exposure of miners is probably different from millers qualitatively. One possibility which has not been evaluated is whether workers were migrants. If this were the case, neither US or local rates would be appropriate and might provide spuriously increased SMRs.

CONCLUSION

1. NTP needs to carefully define what is meant by "Talc Asbestiform".

2. The reason for the overall excess lung cancer in cohorts of GTC workers is still not known. However, it is clear that a statistically significant excess of lung cancer is present in underground miners but not in millers. The lung cancer risk does not increase with increasing tenure or cumulative exposure to respirable GTC talc dust.

3. The evidence does not establish a link between GTC talc exposure and mesothelioma.

4. Collectively the currently available epidemiological studies of GTC workers do not support a causal relationship between GTC talc and respiratory cancer.

5. The currently available epidemiological studies of GTC workers do not support the premise that a causal relationship between GTC and respiratory cancer is credible.

6. In the absence of firm human data establishing a link between GTC talc exposure and respiratory cancer, biologic plausibility depends on an evaluation of the experimental data relating to GTC talc and its constituents. This has not been evaluated in this report.

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Two Submissions to the National Toxicology Program on the

Mineralogy and Experimental Animal Studies of Tremolitic Talc

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An Evaluation of the Epidemiological Evidence Concerning "Talc" and Respiratory Cancer In Humans with Specific Attention to "Talc" as Produced by the Gouverneur Talc Company at its Mines in New York State and Factors to Consider in Evaluating Causation

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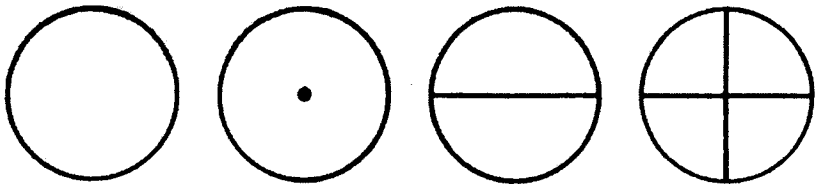
December 1, 2000



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Executive Summary

The nomenclature of asbestiform talc is not specific enough to define a class of carcinogens. The proper nomenclature should be fibrous talc and transitionals. Microscopic analyses indicate the fibrous particulates in talc are not surrogates for asbestos. This fact is further substantiated by the results of several animal studies which indicate significant differences in that fibrous talc and transitionals lack the carcinogenic potency of asbestos fibers. As such, fibrous talc and transitionals do not meet the criteria for inclusion in the NTP Report on Carcinogens and should be removed from further consideration.

Introduction

The nomenclature of asbestiform talc is not specific enough to define a class of carcinogens. An understanding of the mineralogy of tremolitic talc is required to evaluate whether this assemblage of minerals can cause cancer in humans or experimental animals. This is particularly important if you wish to justify the assumption that talc is a surrogate for asbestos as was done in the Report on Carcinogens (ROC Report) Background Document for Talc Asbestiform and Non-Asbestiform. The ROC document reviews the medical and scientific literature and offers a premise for concluding that "talc asbestiform" materials are either "known to be a human carcinogen" or "reasonably anticipated to be a human carcinogen". (Summary of Review Group 1 & 2, ROC, 2000). The two review groups are of differing opinion concerning the evaluation of the information within the background report. Although the summaries are remarkably similar, no explanation for the difference in evaluation is offered, we are of the opinion that neither review group's claim is justified on the basis of the available information for tremolitic talc. Furthermore, the assumption that asbestiform talc is a surrogate for asbestos has not been justified in the ROC document and we will show that such an assumption is not scientifically justifiable.

The medical and scientific literature that the ROC used to describe "talc asbestiform" largely refers to tremolitic talc. This complex assemblage of minerals contains three phases (three different minerals), which can occur as asbestos minerals and two additional minerals that can occur in fibrous form. The ROC relies on relating these

phases to the carcinogenic risks associated with the commercial asbestos minerals to strengthen their case that asbestiform talc is a human and animal carcinogen. We will describe the tremolitic talc mineral assemblage and show that this extrapolation to asbestos is not justified. Examples from experimental animal studies will be used to emphasize the relevance of the mineralogy to carcinogenic risk.

Mineralogy of Tremolitic Talc

New York State tremolitic talc is an assemblage of five principal minerals, which can vary in abundance and particle size to form the various commercial grades (Table 1). Specific grades have properties useful in the fabrication of various products including ceramics and paints. Each grade contains three phases - anthophyllite, tremolite and serpentine – which can exist as asbestos or non-asbestos minerals but asbestos is not typically found in talc (Table 2). The two-amphibole minerals occur more commonly in nature in a nonasbestos habit, although each can occur as asbestos. Commercial deposits of these asbestos minerals have been rare and small and together they represent the least important of the commercial asbestos minerals (Ross, in press). The serpentine asbestos mineral is chrysotile – another serpentine mineral is antigorite, a platy particle. In addition, tremolitic talc can contain two fibrous particulates – fibrous talc sometimes referred to as agalite and an intergrowth of talc and anthophyllite referred to as an intermediate or transitional.

Each of the phases that can occur either as asbestos mineral or as a fibrous particulate was examined and characterized using polarized light microscopy, continuous scan x-ray diffraction and analytical transmission electron microscopy. A variety of tremolitic talc samples and reference standards were used for comparison. NYTAL400, a fine particle size grade of tremolitic talc, which is rich in fibrous particulates, was selected for analysis. Reference standards of the following minerals were selected for comparison:

- NYTAL 400 obtained from Gouverneur Talc Company, Inc., 1837 State Highway 812, Gouverneur, NY 13642.
- Tremolite Asbestos, Korea obtained from John Addison, Cottingham, Hull, United Kingdom.
- Tremolite Nonasbestos Respirable (NTP Animal) obtained from RT Vanderbilt, Inc., 30 Winfield Street, P.O. Box 5150, Norwalk, Ct 06856-5150.
- High Fiber Concentrate obtained from RT Vanderbilt, Inc., 30 Winfield Street, P.O. Box 5150, Norwalk, Ct 06856-5150.
- Anthophyllite Asbestos, UICC, Paakkila, Finland.
- Anthophyllite Asbestos, Anglo Dutch, Republic of South Africa, obtained from Prof DR Bowes.
- Anthophyllite Asbestos, Svedlovsk Region, Russian Federation.

Tremolite

Examination by TEM shows that tremolite particles in the NYTAL 400 tremolitic talc sample range from 20 micrometers to 5 micrometers in length and 1 to 4 micrometers in width with aspect ratios of 6 to 4. The sides of the particles are generally rough and not parallel with irregular to squared off terminations. The width is similar to the thickness indicating the particles are prismatic in shape. The particles are usually too thick to be electron transparent even at 200 keV accelerating voltages. Bright-field images (Figure 1) show the particles to be featureless in areas that were electron transparent.

Selected area electron diffraction patterns of tremolite particles (Figure 2) showed no evidence of disorder or the presence of additional phases or alteration. By tilting on the c-axis open planar fractures can be seen parallel to the c-axis (Figure 3). Selected area electron patterns indicate the open fractures are the {110} cleavage planes.

Fibrous Talc and Transitionals

Examination by TEM shows that fibrous talc particles in the NYTAL 400 tremolitic talc. Fibrous talc is identified in the image by its curved edges, bent and twisted shapes and frayed ends as in flax. It ranges from very thin ribbons with high aspect ratios (Figure 4) to equidimensional mats (Figure 5). Fibrous talc intergrown with anthophyllite appears as relatively straight lath-shaped particulates – commonly with small curved portions of talc-rich material separating from the larger particle at the

sides and ends. In bright-field images long linear features run along the length of the particles (Figure 6). These features are due to diffraction contrast from a talc and anthophyllite intergrowth, these fibrous particulates are the transitional.

Transitionals arise from the alteration of anthophyllite to talc; they are part anthophyllite and part talc intimately intergrown. The compositions of both phases are almost identical so that only an excess of OH^- is needed for the alteration, which easily migrates through the structure. The crystal structures of both phases also are similar so that there is an orientation relationship maintained between anthophyllite and talc. This relationship can be seen in [100] electron diffraction patterns of the transitionals where diffraction from both phases is present (Figure 7). The [100] zone shows layer lines with $l = 3n$ that are intense relative to those with $l \neq 3n$. The addition of the second phase, talc, with its characteristic psuedohexagonal [001] zone axis pattern results in diffraction spot triplets in the $l = 3n$ layer lines. These triplets are characteristic of anthophyllite and talc intergrowths, transitionals, with an interface parallel to (010).

Platy Talc

Talc is a sheet silicate and when growing freely naturally grows fastest parallel to the plane of the sheet as platelets. Sliding between the sheets gives talc its characteristic low hardness and lubricating properties. In the NYTAL 400 talc also occurs as platelets, generally less than 5 micrometers in diameter (Figure 8). A hexagonal arrangement of spots is characteristic of the diffraction pattern (Figure 9).

Serpentine

Serpentine occurs as a platy mineral identified mainly by the high Mg/Si ratio in energy dispersive spectroscopy (EDS) patterns (theoretically 1.5). The serpentine phase is antigorite or lizardite, most likely antigorite, both have a platy habit. No rolled tubes indicative of the chrysotile serpentine mineral (the asbestos variety) were observed.

Anthophyllite

Anthophyllite in the NYTAL 400 sample occurs as tabular crystals similar to popsicle sticks with the large flat face indexed as (100) (Figure 10). The length of the particle is parallel to the c-axis, the width is parallel to the b-axis and the thickness is parallel to the a-axis. This are the same common crystal faces expected in hand-specimen sized anthophyllite crystals. The particles are invariably thin and in most cases electron transparent from one side to the other. Electron diffraction patterns contain no extra spots due to talc alteration (Figure 11 – compare with Figure 7).

The longest particle measured on the sample grid had a length of 200 micrometers and a width of 3 micrometers for an aspect ratio of 67. Aspect ratios of other anthophyllite particles were smaller, ranging down to 2. The width of the smaller particles appeared to be constant at about 2 to 3 micrometers indicating the smaller aspect ratio particles were fragments of larger ones.

The terminations of the anthophyllite particles are generally right angles. Small amounts of alteration material adhering to the terminations indicate the particles break along planes of alteration parallel to (001). Long particles also split along (010) again along bands of alteration. These are seen in images as bands of material that have different diffraction contrast conditions than the adjacent anthophyllite.

Quartz

Quartz in the NYTAL 400 sample occurs as rare irregular shaped featureless particles generally several micrometers in diameter. These were identified by EDS spectra with only Si and O present.

Tremolitic Talc and Experimental Animal Studies

The tremolite present in tremolitic talc are cleavage fragments and should not be referred to as asbestos or asbestiform (Langer et al 1991). Smith et al 1979 evaluated the carcinogenic activity of tremolitic talc, tremolite non-asbestos and tremolite asbestos by intrapleural injections in hamsters. Only tremolite asbestos produced tumors (Table 3, Figure 12) and this is not present in tremolitic talc. The phases present in the tremolitic talc used by Smith et al 1979 were similar to Table 1 in this report with tremolite non-asbestos, talc fibers, talc plates and transitionals (Smith, 1974).

More recently, Davis et al 1991 evaluated six tremolite samples in rats by intraperitoneal injection (see Nolan et al 1991 for a review). Each tremolite sample was prepared as a respirable size range sample. The three-asbestos/asbestiform tremolites produced mesotheliomas in almost all animals. Davis et al 1991 goes on to conclude:

> Two samples of non-fibrous tremolite produced respirable dust samples containing numerous elongated fragments with aspect ratios greater than 3:1, which therefore fitted the definition of respirable fibers. Both these samples produced relatively few tumors, although one had more long "fibers" than did the brittle tremolite that produced 70% tumors. This study has therefore demonstrated that different morphologic forms of tremolite produce dusts with very different carcinogenic potential (p. 489).

Therefore, fibrous morphology alone does not define whether a mineral is carcinogenic or not (Nolan et al, 1991). Stanton et al 1981 reported on 72 experiments relating an index of fiber morphology to carcinogencity. Although the fiber morphology produced some correlation with carcinogenicity it was not without exceptions. For example, two tremolite asbestos samples containing fewer long thin fibers than a fibrous talc sample produced tumor probability of 100% while the fibrous talc produced no tumors (Table 4) (Nolan and Langer, 1993 for a review). Two other platy talc samples tested by Stanton et al 1981 also did not produce

tumors while four other platy talcs produced 1 tumor each corresponding to a tumor probability of 7% or less. The two tremolite asbestos samples which caused tumors are not found in tremolitic talc while fibrous talc which did not produce tumors would be found in tremolitic talc.

Again, there was no increase in the number of tumors in this location, although this procedure appears to have a similar sensitivity as the intraperitoneal injection technique.

The primary animal data set used to classify non-asbestiform talc as an animal carcinogen is the inhalation study conducted by the NTP (NTP 1993). This appears to be a well-conducted and reported study of non-asbestiform talc in rats and mice. The exposure levels (6 and 18 mg/m3) correlate well with the lung burdens in rats although the data for mice are not shown. The concentration of talc in the lungs of the rats increases linearly with dose and time, until 18 months. The evidence for carcinogenic activity is confined to the rat, e.g. the mouse studies were negative. In the rat a significant increase in lung tumors was observed in females, but not males, at 18mg/m3 but not at 6 mg/m3.

However, pheochromocytomas (tumors comprised of chromaffin cells of the adrenal medulla) were increased in both males and females at both exposures. This type of tumor in rats has little relevance to humans because it is related to an epigenetic mechanism as a result of chronic stress related to pulmonary pathology (Tishler et

al., 1988, 1994, 1996, 1999). Chromaffin cell proliferation appears to be under the control of neural signals, which explains tumor formation with the anti-hypertensive drug reserpine (Sietzen et al., 1987). Proof of this mode of action has been offered by Tishler et al. (1994), who showed that chromaffin cell proliferation induced by reserpine could be abolished by adrenal denervation. Pheochromocytomas in rats have also been induced in rats by common food components, e.g. vitamin D, lactose (milk sugar) and xylitol probably as a result of altered calcium homeostasis (Tishler et al., 1999).

Because this type of tumor is such a nonspecific effect and not related to non-asbestiform talc *per se*, it would be interesting to determine how the animal exposures (8 and 16 mg/m3) compare with those encountered by humans. Such information could then be used for margin of exposure analyses, especially since talc is not genotoxic (see below).

Hamsters have also been exposed by inhalation to nonasbestiform talc (talc baby powder) (Wehner et al., 1979). Again, no treatment related tumors were observed, but the study was of too short a duration to make a definitive statement about carcinogenicity.

There was one subcutaneous injection study of talc in mice. No tumors were observed. This is an important study because many solid materials, both fibrous

and nonfibrous particulates cause tumors using this technique and not finding any neoplasms is biologically significant.

The NTP report mentions two intraperitoneal injection studies of non-asbestiform talc in rats, both of which were negative for tumor induction. These are in addition to the negative studies reported earlier for tremolitic talc and some of the various mineral phases of tremolitic talc in rats and hamsters. These are particularly significant result because this technique (route of exposure) is highly sensitive to the induction of tumors (typically mesotheliomas), particularly with fibrous particulates, both naturally occurring and synthetic. In fact, many researchers feel that this technique is overly sensitive and that positive results may not indicate that the mineral phase has a carcinogenic potential for humans. On the other hand, a negative result should be viewed as meaning that it has minimal or no carcinogenic potential. In addition, it needs to be remembered that this technique results in a large and direct exposure to the ovary and surrounding tissues. If talc can cause tumors in this organ, it seems reasonable to expect that tumors would have been found in this exaggerated exposure condition. The negative results of these studies are buttressed by a study in rats where non-asbestiform talc was injected directly into the ovary with no tumor formation (Hamilton et al., 1984).

There was one intrathoracic injection study in mice, which showed a non-significant increase in lymphoid tumors (3/47), and adenocarcinomas (2/47) compared to 0/48 in the concurrent controls. The lymphoid tumors are not biologically significant

because they are not found with other types of fibrous and nonfibrous particulates, including asbestos. The adenocarcinomas are also an unusual response; the typical response is induction of mesotheliomas, none of which were observed.

While the ROC background document attempts to provide a definitive argument for classifying talc as carcinogenic in humans, the summary is not complete in its survey of the medical and scientific literature. For example, the most recent reference in Table 4-6 is 1977. There have been several informative and relevant inhalation studies of fibrous particulates including asbestos in the last 23 years that are not included. The studies undertaken and reported since 1977 represent the state-of-the-art for the inhalation studies of synthetic vitreous fibers in rats and hamsters where different types of asbestos were used as a positive control. If these well-known studies are missing, has other data also been omitted? Furthermore the NTP did not even mention its' own ingestion studies in rats and hamsters of several types of asbestos and non-asbestos tremolite. Finally, why are the talc studies conducted by Stanton using intrapleural instillation and those of Pott using intraperitoneal injection, both of which were negative for tumors, not included in the Table? The review of the medical and scientific literature needs to be re-reviewed and brought up-to-date.

Probably the least justifiable assumption in the ROC background report is the claim that asbestos is a "surrogate for talc". No mineralogical or biological basis has been offered for this assumption. Our review of the medical and scientific literature

indicates the tremolitic talc contains a class of minerals, which are sufficiently different to be considered as a separate and distinct class of minerals from asbestos (see above). It appears that the NTP relies on asbestos-related experimental animal studies to support its claim that talc is carcinogenic in animals because the data specific to asbestiform and non-asbestiform itself is so weak. The weakness of the data may simply reflect that lack of carcinogenic potential in the talc (asbestiform and non-asbestiform) which the ROC report is recommending as either known or probably a human carcinogen.

Genotoxicity

Determining the genotoxicity for particulates and fibers is always problematic because most fibers are relatively insoluble and therefore do not have the same potential to interact with DNA as chemicals. However, it is clear from the data that asbestiform and non-asbestiform talc has not been shown to be genotoxic or clastogenic either *in vitro* or *in vivo*. In contrast, asbestos has been shown to be clastogenic in several types of *in vitro* systems and some *in vivo* ones. The problem is that while the ROC background report states that talc, with or without asbestiform fibers, is not genotoxic, asbestos is and by inference, talc should also be considered positive, in spite of the evidence to the contrary. This is another weakness in the talc as a surrogate for asbestos argument.

Other Relevant Data

The discussion, in this particularly important part of the document, on deposition, clearance and retention is less than thorough. For example, there is no mention of the possibility of dissolution within the body, aspects of surface chemistry or the biological differences between asbestiform and non-asbestiform talc. The report seems to make the argument that because talc particles are found in the lungs and lavage samples from individuals many years after exposure, this means that a potential carcinogenic response is possible. This is a particularly weak argument. For example, using this argument, a coal-miner would be expected to show cancer because coal particles are found in his/her lung or sputum. Well-conducted studies of miners have shown no evidence of coal-related lung cancer, even in the presence of severe pneumoconiosis and high lung burdens. The ROC background report lacks a scientific balance and a modern approach.

Similarly, the document seems to suggest that because talc particulates have been found in ovarian tissues, in both cancerous and normal ovaries, that this indicates cause/effect. At best this is an observation and only of limited value in establishing etiology. One would have to examine ovarian tissue from a large number of individuals, exposed and non-exposed, to make this claim for an etiological role for talc in ovarian cancer. In fact, such a study has been done, and there was no correlation (Heller et al., 1996a, b see ROC Report for reference).

As another example, it is commonly known that asbestos bodies can be found in the lung and lymph nodes of most individuals living in urban environments, there is no evidence to show that such individuals are at an increased risk for asbestos-related cancer, nor do many researches believe these are meaningful risk factors. The most persuasive evidence that talc is not a significant hazard to the ovary is the intraperitoneal injection and intra-ovarian injection studies of huge amounts of talc in rodents. If talc were carcinogenic in this tissue, surely one or more of these studies would have shown a positive result. The ROC background report should be revised to reflect the importance of these animal studies and improve the scientific balance of the report.

Very importantly, in discussing the possible mechanisms of talc toxicity (6.2.2), there are a number of significant reports in medical and scientific literature showing inflammation and resulting production of cytokines and growth factors are important in the mechanism of particulate induced cancer. However, the preeminent investigators in this field, e.g. Driscoll, Kane, Oberdorster, Mossman, etc. are not referenced or their work considered in the document. The ROC report is weak on a state-of-the-art review of mechanisms of fibrous and non-fibrous particulate induced cancer.

Summary

In summary, the document fails to make a case that talc, either asbestiform or non-asbestiform, meets the criteria for inclusion in the NTP Report on Carcinogens. The standard for inclusion of a material into the NTP Report on Carcinogens should be a clearly supported by sound science and judgment establishing the material as a carcinogen. To "list" talc on the basis that asbestos is a "surrogate for talc" is without mineralogical or biological merit and should be rejected.

To the extent that the ROC document relies on asbestos to justify the claim that tremolitic talc is carcinogenic the NTP needs to reconsider their approach. The logic, used within the ROC document, contains conflicts in that the six commercial asbestos minerals are well defined and regulated by OSHA and other regulatory agencies. Such minerals are not exempt from the standard because they occur in association with talc, anymore than they would be exempt because they are used to fabricate a building material. To the extent that commercial asbestos minerals occur in association with talc, exposure would carry the same cancer risk. If the ROC wishes to go beyond simply classifying asbestos as a carcinogen and define other mineral phases present in tremolitic talc as carcinogens they should define the phases that they claiming are carcinogenic – not rely on claims of similarity to asbestos – and produce convincing evidence of carcinogenic effects in human and experimental animals.

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Table 1: Material Safety Data Sheet reports on the composition of tremolitic talc.

	CAS#	% by Weight
Tremolite (nonasbestiform)	14567-73-8	40-60
Talc	14807-96-6	20-40
Serpentine	12135-86-3	15-30
Anthophyllite (nonasbestiform)	17068-78-9	1-10
Quartz	14808-60-7	0.32

Table 2: Ideal formulas for the six regulated asbestos minerals and talc.

Mineral Name	Ideal Chemical Formula	Mineralogical Family/Group
Talc	$Mg_3Si_4O_{10}(OH)_2$	Sheet Silicate
Anthophyllite	$(Mg,Fe^{2+})_7[Si_8O_{22}](OH)_2$	Amphibole Family
Chrysotile	$Mg_3[Si_2O_5](OH)_4$	Serpentine Group
Riebeckite (Crocidolite)	$Na_2Fe_2^{3+}(Fe^{2+},Mg)_3[Si_8O_{22}](OH)_2$	Amphibole Family
Grunerite (Amosite)	$(Mg,Fe^{2+})_7[Si_8O_{22}](OH)_2$	Amphibole Family
Tremolite	$Ca_2Mg_5[Si_8O_{22}](OH)_2$	Amphibole Family
Actinolite	$Ca_2(Mg,Fe^{2+})_5[Si_8O_{22}](OH)_2$	Amphibole Family

Table 3: Results of the interpleural injection of hamsters with tremolitic talc, tremolite non-asbestos and tremolite asbestos (Smith et al, 1979).

	Tumors/survivors[1] Dose: 25 mg			Tumors/survivors[1] Dose: 10mg		
	350 days	**500 days**	**600 days**	**350 days**	**500 days**	**600 days**
Tremolitic Talc	0/35	0/27	0/20	--	--	--
Tremolite Non-Asbestos	0/31	0/15	0/3[2]	0/34	0/14	0/6[3]
Tremolite Asbestos	3/20	5/6	5/1	0/13	1/6	3/2

1 Numerator = cumulative number of hamsters with tumors related to treatment. Denominator = number of survivors.
2 2 additional animals survive.
3 6 additional animals survive.

Table 4: Selected samples from Stanton et al (1981) grouped by mineral name[1]

Mineral	Tumor incidence	Tumor probability (% ± SD)	Log f/μg[†]	Number fibers/μg ≤0.25μm x > 8μm	Total number fibers/μg
Tremolite Asbestos					
1	22/28	100	3.14	1,380	1.41×10^5
2	21/28	100	2.84	692	6.86×10^4
Talc (Asbestiform & Non-Asbestiform)					
1	1/26	7±6.9	--	0	1.26×10^5
2	1/29	4±4.3	--	0	1.26×10^5
3	1/30	4±3.8	--	0	7.43×10^5
4	1/29	5±4.9	--	0	1.90×10^5
5	0/30	0	--	0	2.67×10^5
6	0/30	0	3.3	1,995	3.76×10^5
7	0/29	0	--	0	9.75×10^5

Figure 1: Tremolite particle, 6 μm by 1 μm. (Plate 727)

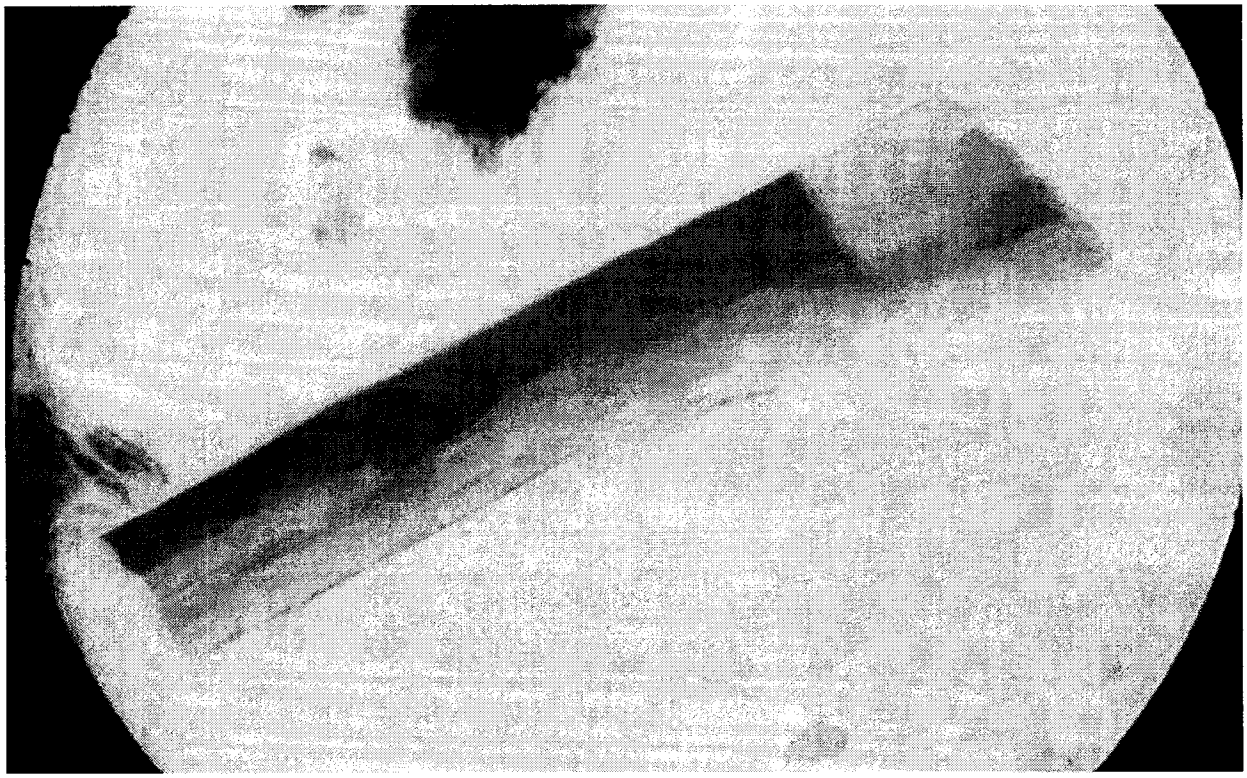


Figure 2: [100] Zone Axis, Selected Area Electron Diffraction Pattern (Plate 724)

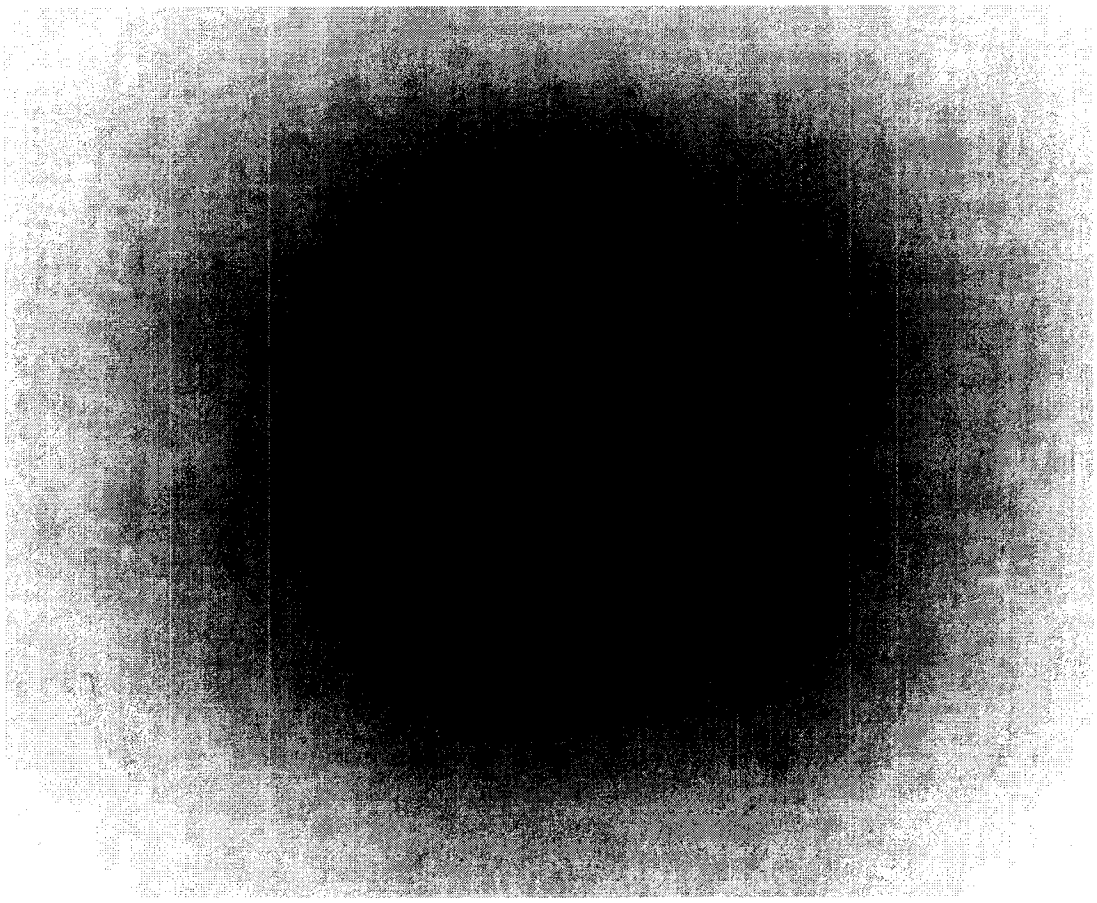


Figure 3: Open Fractures parallel to the c-axis are {110} cleavage planes (Plate 729)

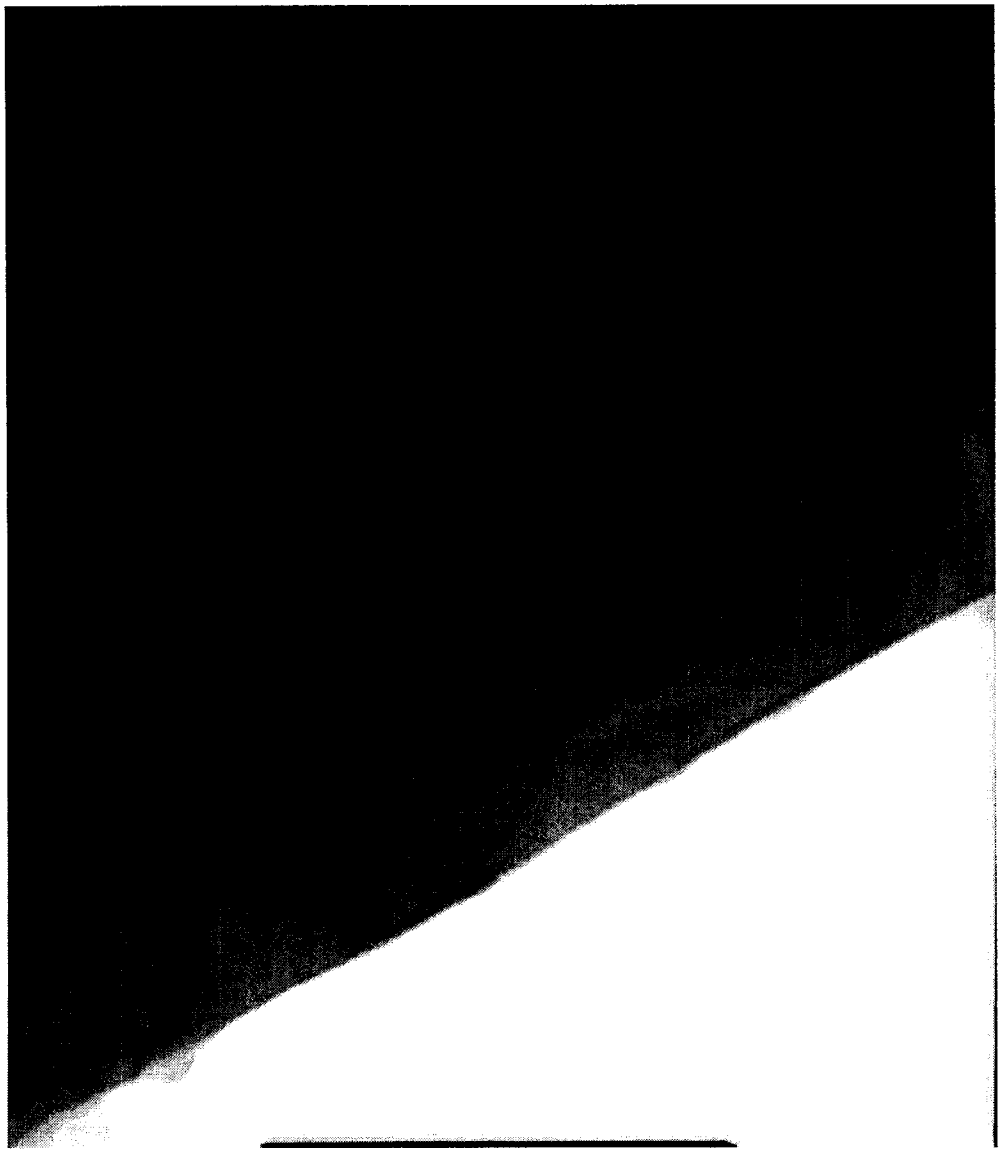


Figure 4: Curved fibrous talc particle with high aspect ratio. (Plate 730)

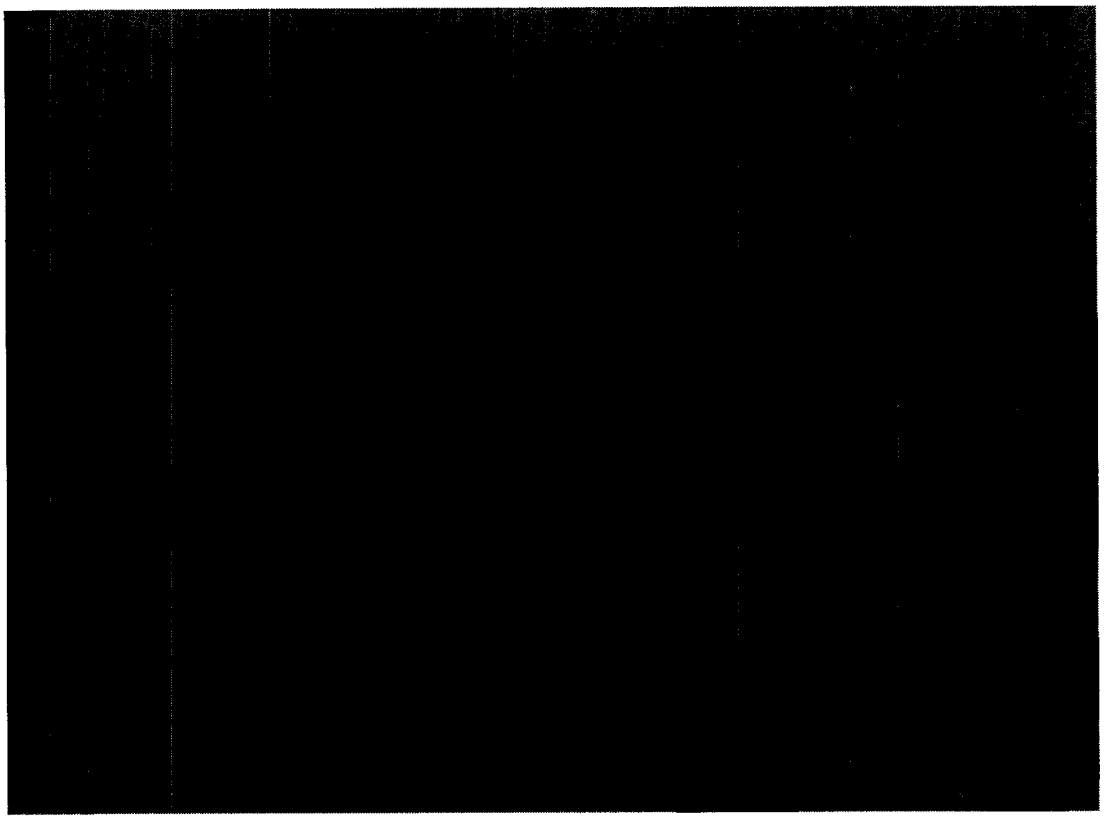


Figure 5: Fibrous talc particle (Plate 531)

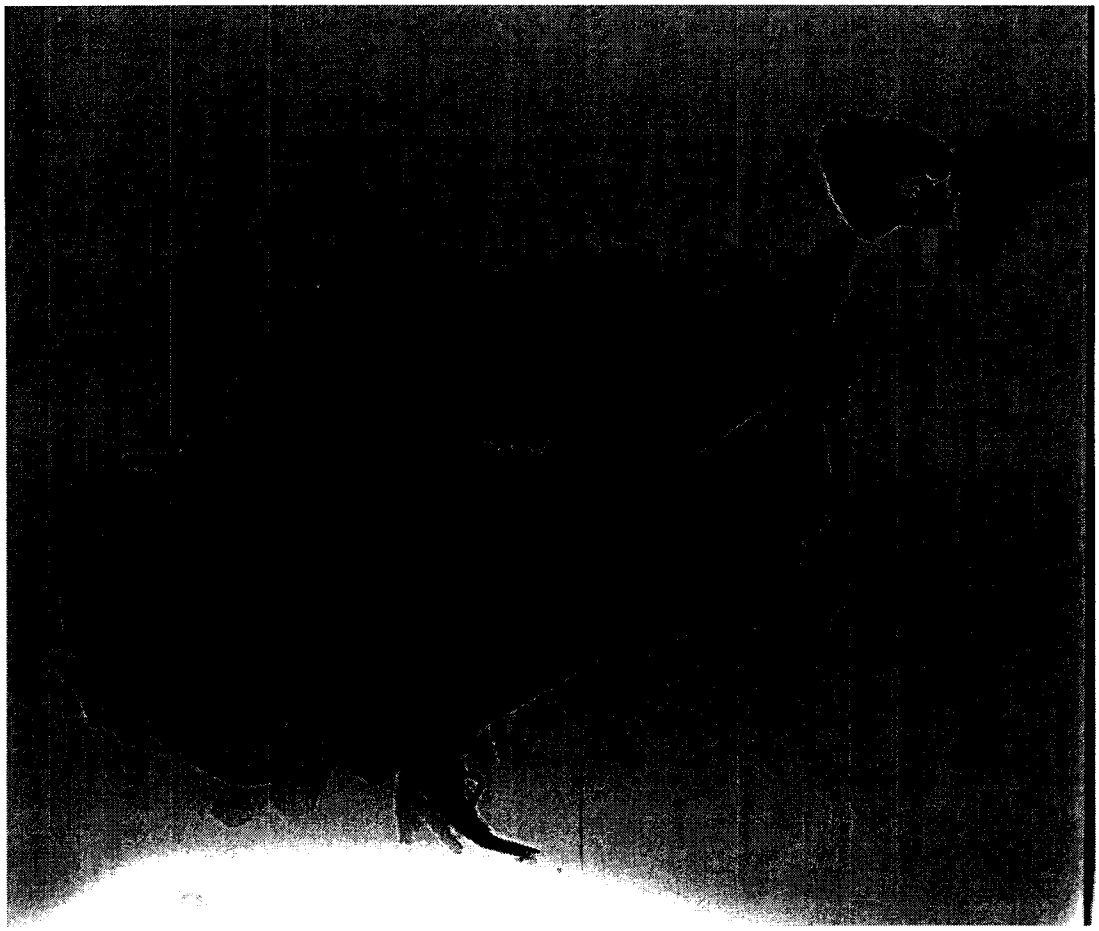


Figure 6: "Transitional" showing linear features from the intergrowth. (Plate 686)

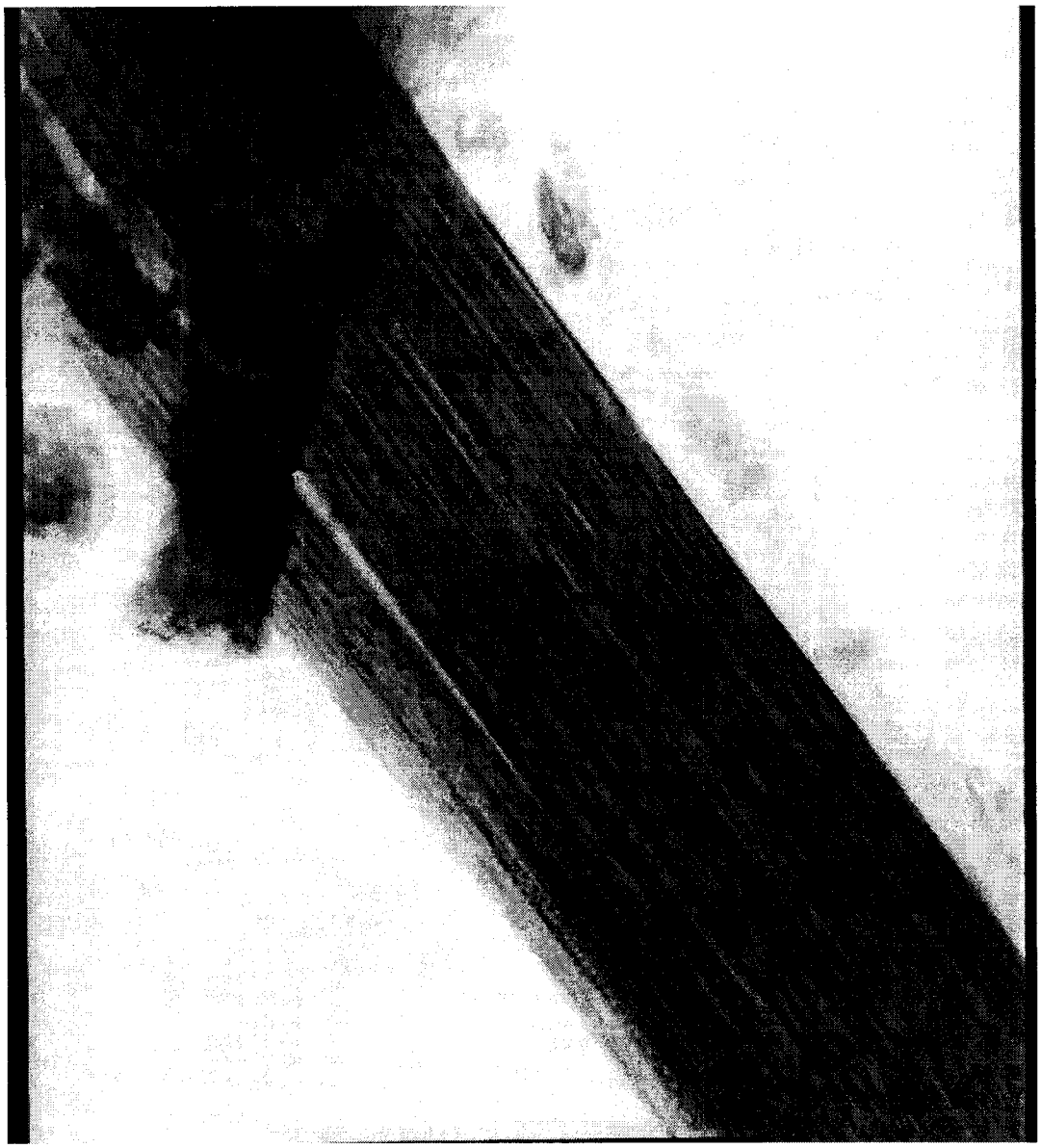


Figure 7: [001] Zone Axis showing both anthophyllite and talc spots in "Transitional" particle. (Plate 562)

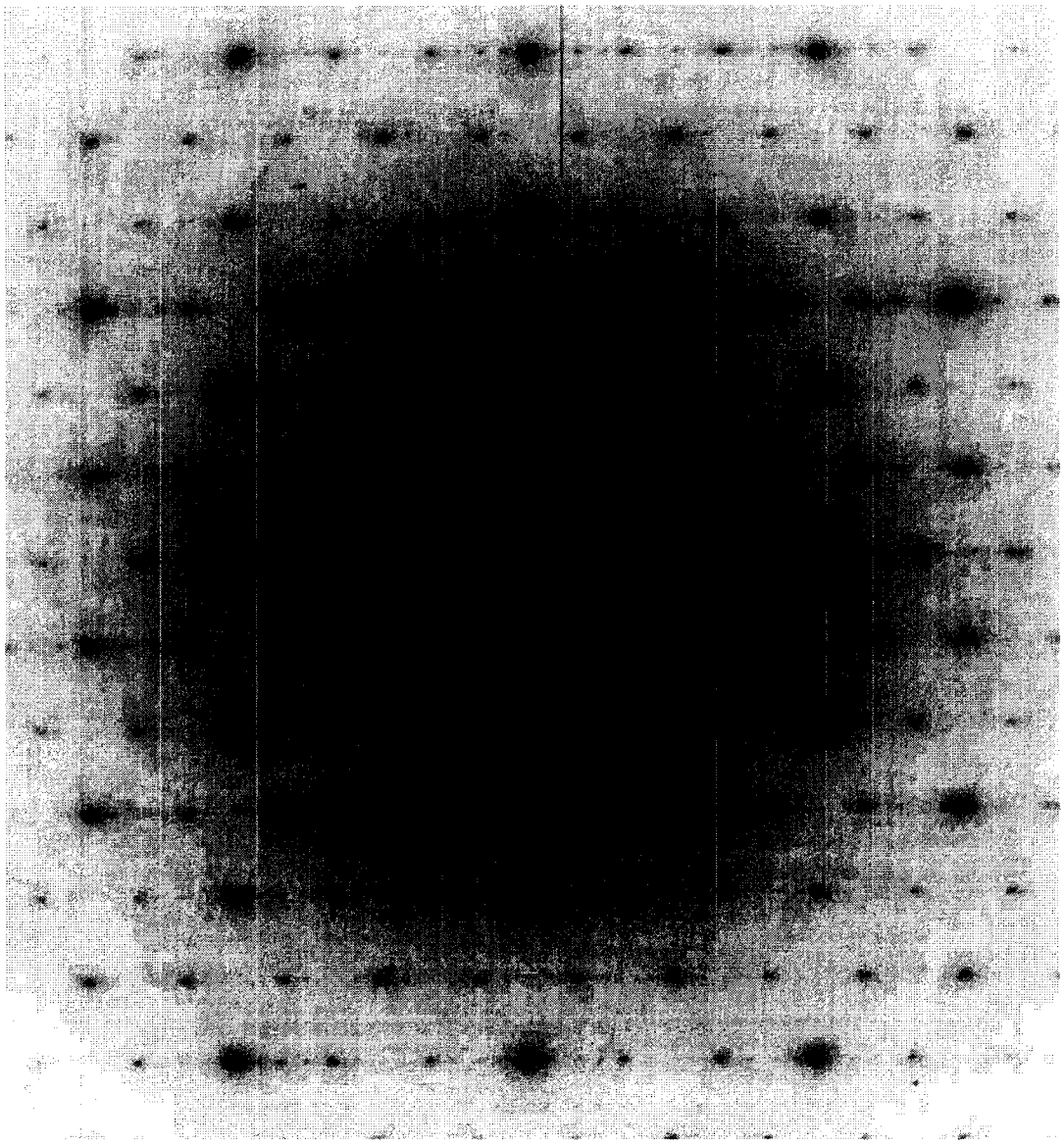


Figure 8: Talc Plate (Plate 706)

Figure 9: [001] Zone Axis from Talc Plate (Plate 707)

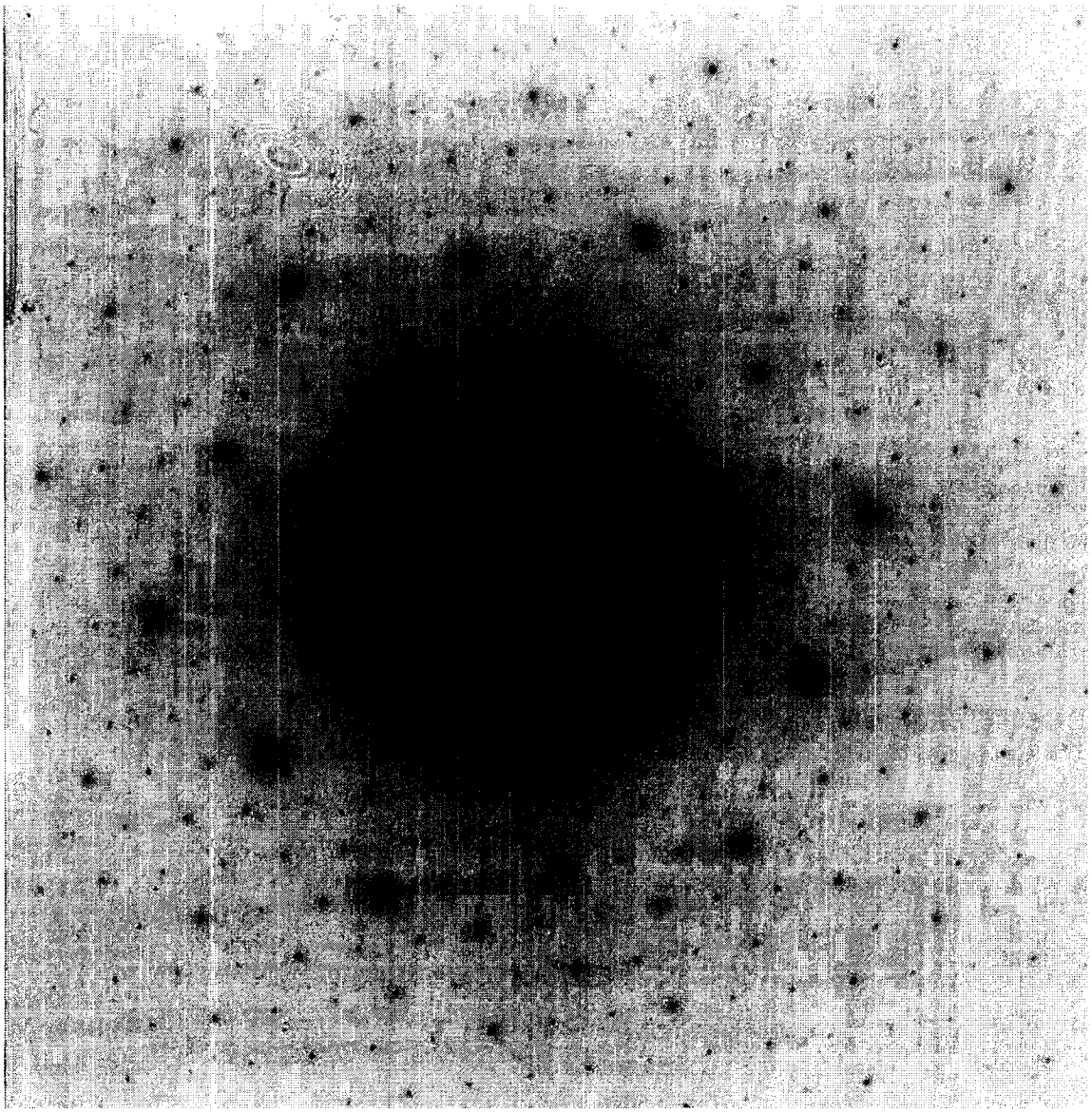


Figure 10: Bright Field electron micrograph of an anthophyllite particle. The width is 0.5 micrometers and the length is 6 micrometers with an aspect of 12. (Plate 709)

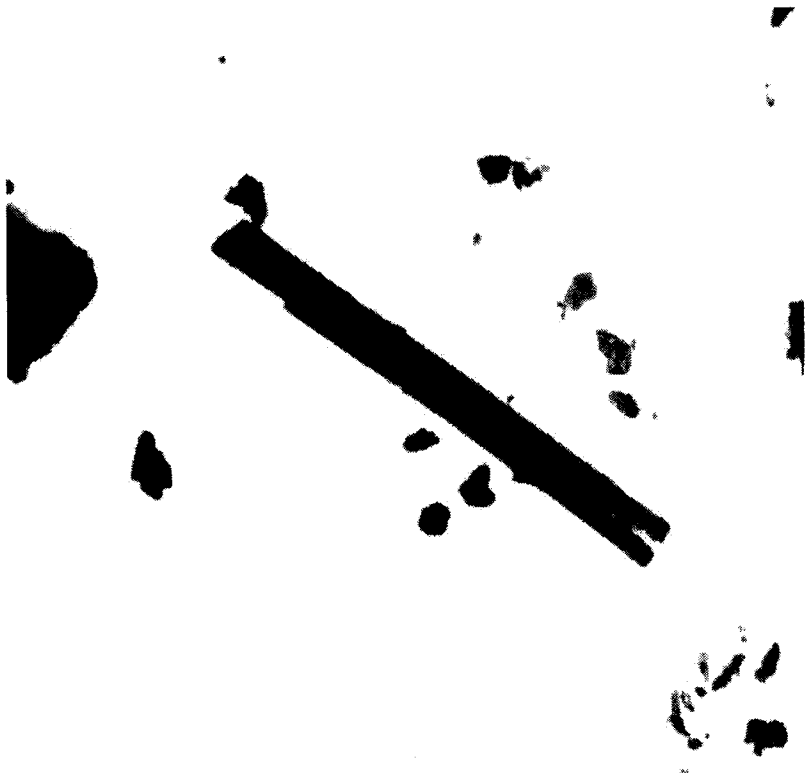
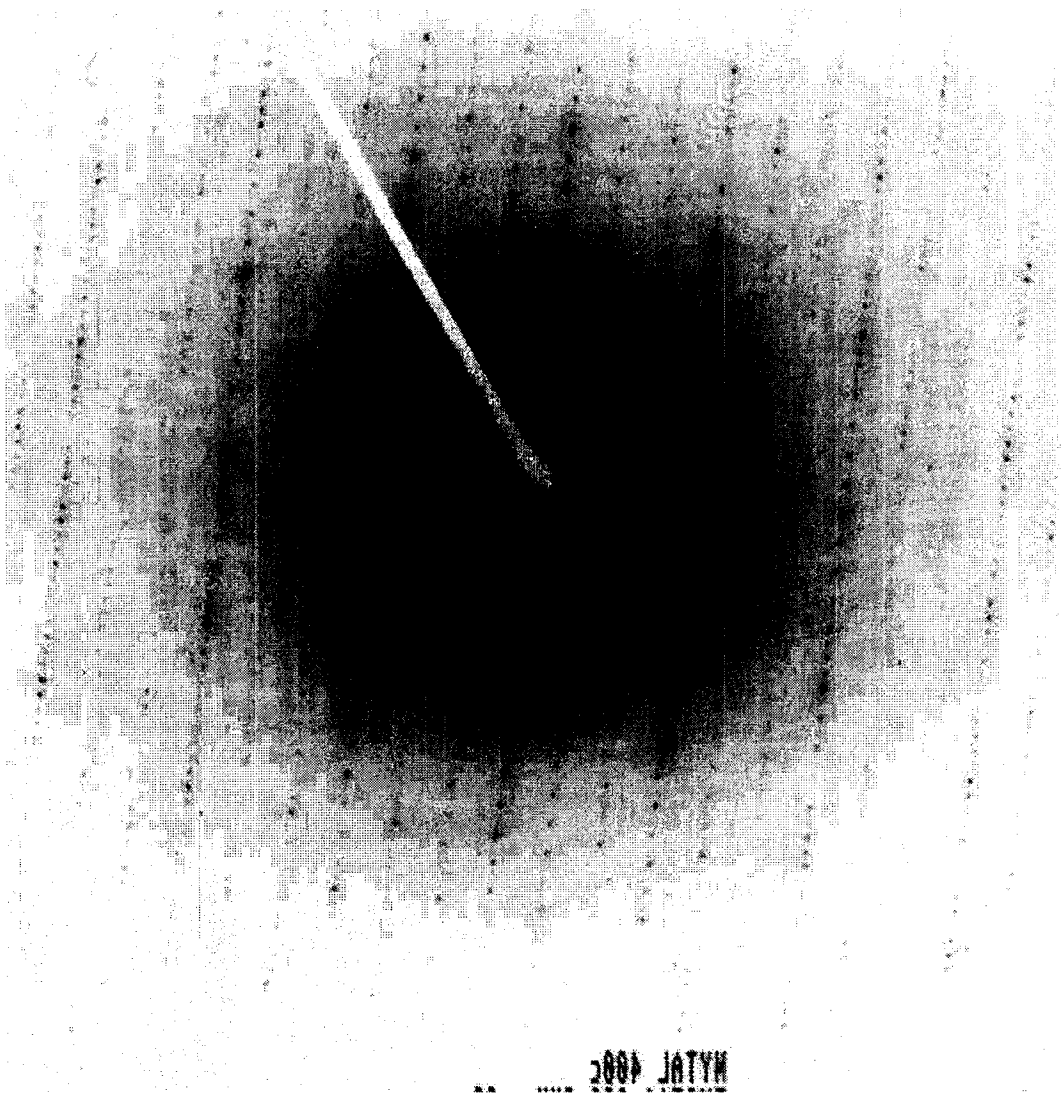


Figure 11: Selected area electron diffraction pattern of the [100] zone axis. Very weak spots from intergrown talc are also present. (Plate 711)



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Mr. Bruce Mandel
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March 17, 1995

Dear Mr. Mandel;

I have studied the relationship between mineralogy and health effects for more than 20 years. During this time, I have read the literature extensively and studied many minerals that have been implicated in disease.

Over the last fifteen years, I have analyzed numerous samples from the Gouverner Talc District in New Your State including raw ore, fiber concentrates and commercial products. These analyses have been conducted with both optical and electron microscopy.

The major minerals found in the commercial talc deposits from the Gouvernor Talc District are talc, serpentine, tremolite, fibrous talc and small amounts of other silicates such as quartz and anthophyllite. I have not detected asbestos in the samples I have examined.

I am familiar with animal studies using fibrous minerals especially the work of Merle Stanton which was designed to investigate the relationship between the dimensions of durable mineral fibers and mesothelioma. I have examined many of the samples he used and I have identified the source of all the talc samples. Two of the talc samples were from The Gourvernor district of New York State. In the Stanton experiments the Gouvernor talc samples did not cause statistically significant excess cancer.

Sincerely yours,

Ann G. Wylie

Ann G. Wylie
Professor